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Linking within- and between-host scales for understanding the evolutionary dynamics of quantitative antimicrobial resistance

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Abstract

Understanding both the epidemiological and evolutionary dynamics of antimicrobial resistance is a major public health concern. In this paper, we propose a nested model, explicitly linking the within- and between-host scales, in which the level of resistance of the host population is viewed as a continuous quantitative trait. The within-host dynamics is based on integro-differential equations structured by the resistance level, while the between-host scale is additionally structured by the time since infection. This model simultaneously captures the dynamics of the bacteria population, the evolutionary transient dynamics which lead to the emergence of resistance, and the epidemic dynamics of the host population. Moreover, we precisely analyze the model proposed by particularly performing the uniform persistence and asymptotic results. Finally, we discuss the impact of the treatment rate of the host population in controlling both the epidemic outbreak and the average level of resistance, either if the within-host scale therapy is a success or failure. We also explore how transitions between infected populations (treated and untreated) can impact the average level of resistance, particularly in a scenario where the treatment is successful at the within-host scale.

Key words. Antimicrobial resistance; Evolutionary dynamics; Nested models; Non-linear dynamical system.

1 Introduction

Antimicrobial resistance (AMR) is one of the major challenges we face in the modern area [1, 30]. An antimicrobial substance is a chemical agent interacting with the physiology of a bacterial cell. The antimicrobial activity on a given bacterium's survival (\mathcal{S}) is an increasing function of its concentration in the medium (\mathcal{C}), such that $\mathcal{S}(0) = 0$ and $\mathcal{S}(\mathcal{C}) \rightarrow \mathcal{S}_{\text{sat}}$ as $\mathcal{C} \rightarrow \mathcal{C}_{\text{sat}}$, where \mathcal{S}_{sat} and \mathcal{C}_{sat} are saturating constants. This intuitive approach implies that there exists \mathcal{C}^* in $(0, \mathcal{C}_{\text{sat}})$ such that $\mathcal{S}(\mathcal{C}^*)$ is equal to the intrinsic rate of increase and reverses the growth of a bacterial population. Such a threshold concentration at which a bacterial population does not grow (at least in *in vitro*) is called the Minimum Inhibitory Concentration (MIC). The level of resistance to a given antimicrobial is then a continuous trait by nature referred to as antimicrobial quantitative resistance (qAMR), and qAMR is key to better understand the evolutionary dynamics of AMR [17]. Here, we introduce a quantitative descriptor $x \in \mathbb{R}$ – a label of the bacterial strain with resistance level x – describing the level of resistance. Most of the modelling approaches devoted to AMR tackling the case of qualitative (or “binary”) resistance are generally based on the dynamical interaction between two parasite strains leading to a binary MIC formulation [6]. This analysis ignores the evolutionary short-term transient dynamics which lead to the emergence of resistance. We think that the literature is so vast that we would not know where to begin since the model used then strongly depends on the question asked (*eg.*, [12, 13, 15, 29, 31, 39, 42]).

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Here, we proposed a nested (or embedded) model explicitly linking the within- and between-host evolutionary dynamics. Such a nested structure is particularly important because, over the past few decades, it is clear that ecological and evolutionary dynamics are influenced by processes operating across scales [20]. Very few studies considered the continuous nature of AMR in the context of this work (*eg.*, [17]), and few studies have implemented a nested model in this context so far (*eg.*, [5, 40]). At the within-host scale, the model proposed is based on integro-differential equations, and the model follows the dynamics of a bacterial population within either a treated host (b^T) or untreated host (b^U). The bacterial population is assumed to be phenotypically (and genetically) diverse through the level of antimicrobial resistance x . This quantitative trait affects different components of the bacterial population life cycle, such as growth and death rates. In addition to those effects on the death and birth rates, bacterial population resistance level also mitigates the antimicrobial efficiency with respect to that population. From a theoretical point of view, properties of the within-host model proposed here are based on previous analytical quantitative genetics results developed in [9, 16]. The main variables and parameters of the within-host model are listed in Table 1. At the between-host scale, the host population is subdivided into three states. At any time t , an individual –with the immune system’s response level $i \in \mathcal{I} = \{1, \dots, n\}$ – can be susceptible to the infection $S_i(t)$, infected since time τ by a bacteria with resistant level x and be either a treated infection $I_i^T(t, \tau, x)$ or untreated $I_i^U(t, \tau, x)$. Individual transmission probability τ -time since infection, $\beta_i^\vartheta(\tau, x)$, is linked to the individual’s within-host dynamics such that, $\beta_i^\vartheta(\tau, x) = \beta_i^\vartheta [b_i^\vartheta(\tau, x)]$. Similarly, the loss rate of infected individuals, α_i^ϑ , is also linked to the individual’s within-host dynamics such that, $\alpha_i^\vartheta(\tau, x) = \alpha_i^\vartheta [b_i^\vartheta(\tau, x)]$. The main variables and parameters of the within-host model are listed in Table 1. The nested model proposed here then allows for simultaneous track the epidemiological dynamics of the host population as well as evolutionary quantities such as the average level of resistance at both the within- and between-host scales. Such an approach is original and to our knowledge, no study has considered nested models for the evolutionary dynamics of AMR, viewed as a continuous quantitative trait.

An integro-differential equation is used to model the within-host dynamics of the bacterial population. Such a within model formulation is previously proposed in [17]. Any host individual is either a treated host (labelled T) or an untreated host (labelled U). At any time τ , the bacteria density with resistance level $y \in \mathbb{R}$ within a treated and untreated host is quantified by $b_i^T(\tau, y)$ and $b_i^U(\tau, y)$ respectively. The subscript “ i ” (with $i \in \mathcal{I} = \{1, 2, \dots, n\}$) represents an individual immune system and then allows taking into account the immune system heterogeneity in the host population. A bacteria with resistance level y generate offspring with resistance level x at a per-capita rate $J(x - y)p_i(y)b_i^\vartheta(\tau, y)$, where $p_i(y)$ is the bacterial intrinsic growth rate, and $J(x - y)$ is the probability for a bacterial population with resistance level y to mutate towards a level x during the reproduction process. Therefore, the total number of bacteria produced at time τ with a resistance level x is quantify by $(1 + \int_{\mathbb{R}} b_i^\vartheta(\tau, x)dx)^{-\kappa} \int_{\mathbb{R}} J(x - y)p_i(y)b_i^\vartheta(\tau, y)dy$, where κ is a positive parameter. The parameter $\kappa > 0$ is introduced to impose the bacterial population homeostasis. The within-host model reads as

$$\begin{cases} \partial_\tau b_i^\vartheta(\tau, x) = \frac{1}{(1 + B_i^\vartheta(\tau))^\kappa} \int_{-\infty}^{+\infty} J(x - y)p_i(y)b_i^\vartheta(\tau, y)dy - \xi_i^\vartheta(x)b_i^\vartheta(\tau, x), \\ b_i^\vartheta(0, \cdot) = b_{i0}^\vartheta(\cdot), \end{cases} \quad (1.1)$$

where $B_i^\vartheta(\tau) = \int_{-\infty}^{+\infty} b_i^\vartheta(\tau, x)dx$, is the total bacteria load. The term ξ_i^ϑ accounts for the clearance of the bacterial population with resistance level x , either by the immune system (μ_i^ϑ) or by the efficiency of antimicrobial pressure (k_i). Thus, $\xi_i^U(x) = \mu_i^U(x)$, for untreated host, and $\xi_i^T(x) = \mu_i^T(x) + k_i(x)$, for treated host.

At the between-host level, the host population is subdivided into three states. At the time t , an individual (with the immune response level i) can be susceptible to the infection $S_i(t)$, infected by a bacteria with resistant level x . Such an individual infection (infected since time τ) can be either treated $I_i^T(t, \tau, x)$ or untreated $I_i^U(t, \tau, x)$. The force of infection underwnt by susceptible individuals at time t

is then given by

$$\bar{\lambda}(t, x) = \sum_{i \in \mathcal{I}} \int_0^\infty [\beta_i^T(b_i^T(\tau, x))I_i^T(t, \tau, x) + \beta_i^U(b_i^U(\tau, x))I_i^U(t, \tau, x)]d\tau.$$

However, an infected individual with a resistance level y , will induce a new infection with a resistance level x by the probability $K(x - y)$. Such a probability is assumed to be the same for both treated and untreated infections. Consequently, the disease is effectively transmitted by the quantity

$$\lambda(t, x) = \int_{\mathbb{R}} K(x - y)\bar{\lambda}(t, y)dy.$$

The dynamics of newly infected individuals (*i.e.* $\tau = 0$) in each group (treated or untreated) is thus defined by (for $\vartheta \in \{T, U\}$)

$$I_i^\vartheta(t, \tau = 0, x) = p_i^\vartheta(x)\lambda(t, x)S_i(t), \quad (1.2)$$

where the treatment rate in the host population $p_i^T(x)$ is assumed to depend on the bacterial population resistance level x , and $p_i^U(x) = 1 - p_i^T(x)$. During their infection, treated individuals can stop the treatment at rate $\omega_U^T(\tau, x)$, and untreated infections can join the treated group at rate $\omega_T^U(\tau, x)$. The loss rate of infected individuals, infected since time τ with a resistance level x , occurs at rate $\alpha_i^\vartheta(\tau, x)$. The whole population died naturally at rate μ_h . The between-host model then reads

$$\begin{cases} \dot{S}_i(t) = \Lambda_i - S_i(t) \int_{\mathbb{R}} \lambda(t, x)dx - \mu_h S_i(t), \\ (\partial_t + \partial_\tau) I_i^T(t, \tau, x) = -(\alpha_i^T(\tau, x) + \omega_U^T(\tau, x) + \mu_h) I_i^T(t, \tau, x) + \omega_T^U(\tau, x) I_i^U(t, \tau, x), \\ (\partial_t + \partial_\tau) I_i^U(t, \tau, x) = -(\alpha_i^U(\tau, x) + \omega_T^U(\tau, x) + \mu_h) I_i^U(t, \tau, x) + \omega_U^T(\tau, x) I_i^T(t, \tau, x), \\ S_i(0) = S_{i,0}, \quad I_i^\vartheta(0, \tau, x) = I_{i,0}^\vartheta(\tau, x). \end{cases} \quad (1.3)$$

Finally, the nested within-host (1.1) and the between-host model (1.2)-(1.3) are summarised by Figure 1.

Model (1.1)-(1.3) will be considered under the following assumptions. Parameters β_i^ϑ and α_i^ϑ , with $\vartheta \in \{T, U\}$, are such that

Assumption 1.1 1. $\beta_i^\vartheta(0) \geq 0$, $(\beta_i^\vartheta(b_i^\vartheta))' > 0$ and $(\beta_i^\vartheta(b_i^\vartheta))'' \leq 0$.

2. $\alpha_i^\vartheta(0) \geq 0$, $(\alpha_i^\vartheta(b_i^\vartheta))' > 0$ and $(\alpha_i^\vartheta(b_i^\vartheta))'' \leq 0$.

Here we recall that, for simplicity, we will sometimes use the following equivalencies $\beta_i^\vartheta(\tau, x) \equiv \beta_i^\vartheta(b_i^\vartheta(\tau, x))$ and $\alpha_i^\vartheta(\tau, x) \equiv \alpha_i^\vartheta(b_i^\vartheta(\tau, x))$.

Moreover, parameters β_i^ϑ and α_i^ϑ can be defined using Holling type functional responses. The first example is the Holling functional response of type I, assuming a linear increase of the transmission probability and virulence with respect to the bacterial density within the infected host such that,

$$\beta_i^\vartheta(\tau, x) = \beta_0 b_i^\vartheta(\tau, x) \quad \text{and} \quad \alpha_i^\vartheta(\tau, x) = \alpha_0 b_i^\vartheta(\tau, x).$$

Another example is the Holling functional response of type II (or similarly the Beddington-DeAngelis functional response) such that

$$\beta_i^\vartheta(\tau, x) = \frac{\beta_0 b_i^\vartheta(\tau, x)}{r_0 + b_i^\vartheta(\tau, x)} \quad \text{and} \quad \alpha_i^\vartheta(\tau, x) = \frac{\alpha_0 b_i^\vartheta(\tau, x)}{r_0 + b_i^\vartheta(\tau, x)}, \quad (1.4)$$

where β_0 and α_0 are scaling constants, and r_0 is the half-saturation constant for the bacterial load. In this later example, the transmission probability and the virulence of an infected host increase monotonically

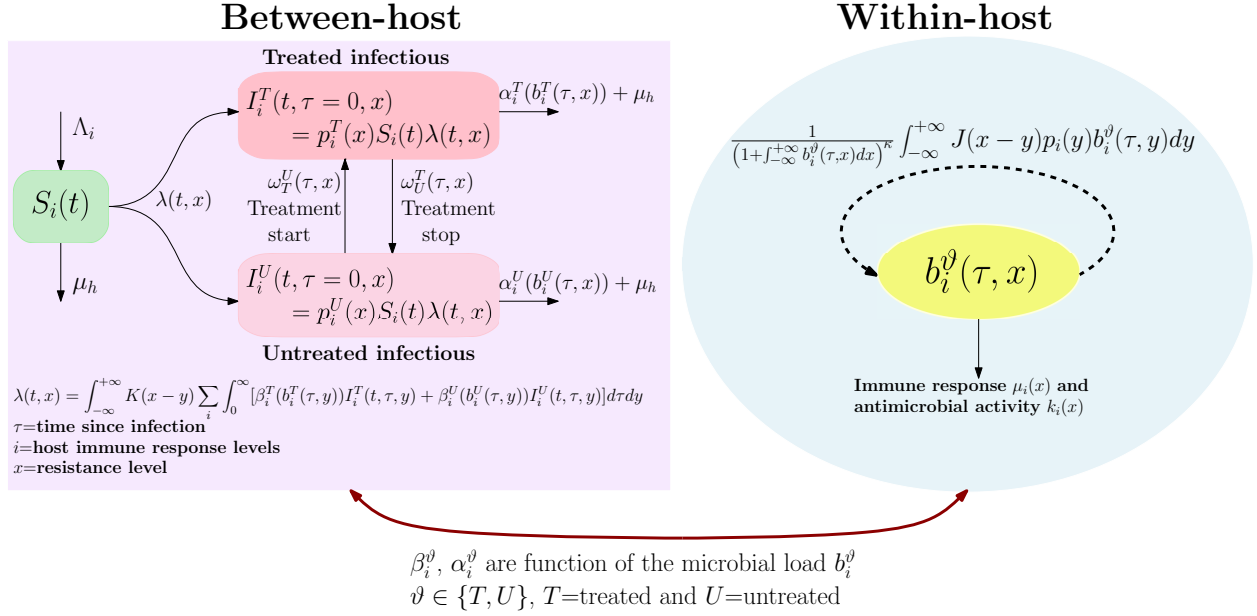


Figure 1: Flow diagram of the nested model. **Within-host model:** The number of bacteria produced at time τ with resistance level x is $\frac{1}{(1 + \int_{-\infty}^{+\infty} b_i^\vartheta(\tau, x) dx)^\kappa} \int_{-\infty}^{+\infty} J(x-y) p_i(y) b_i^\vartheta(\tau, y) dy$, where $J(x-y)$ is the probability for a bacterial with resistance level $y \in \mathbb{R}$ to mutate towards a level $x \in \mathbb{R}$ and $p_i(y)$ is the bacterial intrinsic growth rate. A bacterial population with resistance level x , within an individual with immune system level i , is cleared either by the immune system at rate $\mu_i^\vartheta(x)$ or by the antimicrobial efficiency at rate $k_i(x)$. **Between-host model:** Susceptible individuals are recruited at a constant rate Λ_i . Infectious individuals at time t , which are infected since time τ , are in two states, either treated ($I_i^T(t, \tau, x)$) or untreated ($I_i^U(t, \tau, x)$). The force of infection in the whole population at time t is $\lambda(t, x) = \int_{\mathbb{R}} K(x-y) \sum_{i \in \mathcal{I}} \int_0^\infty [\beta_i^T(b_i^T(\tau, y)) I_i^T(t, \tau, y) + \beta_i^U(b_i^U(\tau, y)) I_i^U(t, \tau, y)] d\tau dy$, with $\beta_i^\vartheta(b_i^\vartheta(\tau, x))$ the probability of disease transmission of an infected individual with a bacterial load $b_i^\vartheta(\tau, x)$. At the time t , new infections with resistance level x occur at rate $\lambda(t, x) S_i(t)$, and are either treated with a probability $p_i^T(x)$ or untreated with a probability $p_i^U(x)$. The natural death rate of individuals is μ_h . If infected since time τ , the disease induced mortality is $\alpha_i^\vartheta(b_i^\vartheta(\tau, x))$. Untreated individuals with a resistance level x , and infected since time τ start the treatment at rate $\omega_T^U(\tau, x)$ while treated individuals stop the treatment at rate $\omega_T^T(\tau, x)$.

with the within-host bacterial load, but their increase would be slower than the linear formulation for higher bacteria density.

The rest of this work is organized as follows. In Section 2, we state the main results of the nested model that are obtained in this work. These include the existence of the globally defined non-negative semiflow and the existence of the unique positive equilibrium for the within-host model, and threshold analysis results for the between-host model. The model's typical dynamics and discussion are provided in Section 3. This includes the within- and between-host models parameterization, the characterization of the evolutionary parameters such as the average levels of resistance for bacterial and host populations, and the impacts of some parameters on host population structure at equilibrium. Section 4 is dedicated to preliminaries results. More precisely, the existence and uniqueness of solutions, the derivation of the basic reproduction number as well as the existence of a unique endemic equilibrium of System (1.2)-(1.3). Section 5 is devoted to the proof of the main result stated by Theorem 2.7.

Table 1: Within- and between-host model variables and parameters

Notations	
t	Time
τ	Time since infection (infection age)
x	Resistance level
i	host immune response level
Model state variables	
Within-host	
$b_i^T(\tau, x)$	Density of treated bacterial population with resistance level x at time τ
$b_i^U(\tau, x)$	Density of untreated bacterial population with resistance level x at time τ
Between-host	
$S_i(t)$	Susceptible humans at time t
$I_i^T(t, \tau, x)$	Treated infected humans, infected since time τ , with resistance level x
$I_i^U(t, \tau, x)$	Untreated infected humans, infected since time τ , with resistance level x
Model parameters	
Within-host	
$J(x - y)$	Mutation probability from resistance level x to y per cell division
$p_i(x)$	Intrinsic growth rate of bacterial population with resistance level x
$k_i(x)$	Killing rate of bacterial population with resistance level x due to drug
$\mu_i^\vartheta(x), \vartheta \in \{T, U\}$	Clearance rate of the bacterial population with resistance level x due to the immune response
Between-host	
$\beta_i^T(\tau, x)$	Transmission rate of treated infected
$\beta_i^U(\tau, x)$	Transmission rate of untreated infected
$\alpha_i^T(\tau, x)$	Treated infected death rate induced by the infection
$\alpha_i^U(\tau, x)$	Untreated infected death rate induced by the infection
$\omega_U^T(\tau, x)$	Rate of treatment cessation
$\omega_T^U(\tau, x)$	Rate of treatment start
$p_i^T(x)$	Treatment rate

2 Main results

This section is devoted to the main results of the nested model (1.1)-(1.3). Such results include the existence of the unique maximal bounded semiflow, and a precise description of the unique positive equilibrium of Model (1.1). By providing local stability results, we will also conduct a precise threshold analysis of the between-host model (1.2)-(1.3).

First of all, for biological feasibility of the between-host model (1.2)-(1.3), the model's parameters satisfy the following assumption for $i \in \mathcal{I}$.

Assumption 2.1 1. Recruitment rate Λ_i and natural death rate μ_h are positive constants.

2. The functions $p_i^\vartheta \in L_+^\infty(\mathbb{R})$ are continuous and bounded.

3. The rates ω_U^T, ω_T^U belongs to $L_+^\infty(\mathbb{R}_+ \times \mathbb{R})$, with respective essential upper bounds $\bar{\omega}_U^T, \bar{\omega}_T^U$ and positive essential lower bounds $\underline{\omega}_U^T, \underline{\omega}_T^U$ for each $(\tau, x) \in \mathbb{R}_+ \times \mathbb{R}$.

Furthermore, the within-host model (1.1) is formulated based on the following assumption

Assumption 2.2 1. Functions $\mu_i^\vartheta, k_i, \xi_i^\vartheta$, and p_i are always positive on \mathbb{R} , with $\vartheta \in \{T, U\}$. Furthermore, p_i is a bounded function on \mathbb{R} and $\kappa > 0$. Finally, the function $\frac{p_i}{\xi_i^\vartheta}$ is continuous on \mathbb{R} and satisfies $\frac{p_i}{\xi_i^\vartheta} > 0$ and $\lim_{|x| \rightarrow \infty} \frac{p_i}{\xi_i^\vartheta}(x) = 0$.

2. The mutation kernel J is bounded and integrable on \mathbb{R}^+ , positive almost everywhere, and satisfies $\int_{\mathbb{R}^+} J(x) dx > 0$, $J(-x) = J(x)$, for all x .

3. The mutation kernel J decays rather rapidly towards infinity in the sense that $J(x) = O\left(\frac{1}{|x|^\infty}\right)$ as $|x| \rightarrow \infty$. In other words, $\lim_{|x| \rightarrow \infty} |x|^n J(x) = 0$, for all $n \in \mathbb{N}$.

The dynamical properties of the within-host model (1.1) have been precisely investigated in [17]. Here we recall such results and refer to [17] for more details about their proof. The first result of Model (1.1) is about the existence of the unique maximal bounded semiflow. Such a result reads as,

Theorem 2.3 Let Assumption 2.2 be satisfied. Let $b_{i0}^\vartheta \in L_+^1$. Then,

1. There exists a unique global solution $v(\cdot, b_{i0}^\vartheta) : [0, \infty) \rightarrow L_+^1(\mathbb{R})$ of (1.1) with $v(0, b_{i0}^\vartheta) = b_{i0}^\vartheta$ and $v(\tau, b_{i0}^\vartheta) = b_i^\vartheta(\tau, \cdot)$ for all $\tau > 0$.

2. The semi-flow defined by $\{v(\tau, b_{i0}^\vartheta)\}_\tau$ is bounded dissipative and asymptotically smooth, and hence, it admits a global attractor in $L_+^1(\mathbb{R})$.

3. The semi-flow $\{v(\tau, b_{i0}^\vartheta)\}_\tau$ is such that for any $b_{i0}^\vartheta \in L_+^1(\mathbb{R}) \setminus \{0\}$, $b_i^\vartheta(\tau, x) > 0$, for all $\tau > 0$, $x \in \mathbb{R}$.

Since the within-host densities b_i^ϑ, s are bounded (Theorem 2.3) and differentiable with respect to τ , by Assumption 1.1 we have the following remark.

Remark 2.4 (i) Transmission rates β_i^ϑ, s are Lipschitz continuous almost everywhere on $L_+^1(\mathbb{R})$.

(ii) Mortality rates α_i^ϑ, s are such that there exists a constant $\bar{\alpha}_0 > 0$ so that $\alpha_i^\vartheta(\tau, x) < \bar{\alpha}_0$ for each $(\tau, x) \in \mathbb{R}_+ \times \mathbb{R}$.

The basic reproduction number $\mathcal{N}_{i0}^\vartheta$ – defined as the expected number of bacteria arising from one bacterium in a bacteria-free environment – of the bacteria population with resistance level x , within an individual with immune system level i , is calculated as

$$\mathcal{N}_{i0}^\vartheta(x) = \frac{p_i(x)}{\xi_i^\vartheta(x)}, \text{ for } \vartheta \in \{U, T\}. \quad (2.1)$$

Next, a non-trivial equilibrium of Model (1.1) is strongly related to the principal eigenpaire of the below linear integral operator H_i^ϑ defined on $L^p(\mathbb{R})$ (for any $p \geq 1$), by

$$H_i^\vartheta[v_i^\vartheta](x) = \sqrt{\mathcal{N}_{i0}^\vartheta(x)} \int_{\mathbb{R}} J(x-y) \sqrt{\mathcal{N}_{i0}^\vartheta(y)} v_i^\vartheta(y) dy. \quad (2.2)$$

We then have the following result.

Theorem 2.5 *Let $r(H_i^\vartheta)$, the spectral radius of the operator H_i^ϑ , and $\phi > 0$ the associated eigenfunction normalized such that $\|\phi\|_{L^1} = 1$.*

1. *When $r(H_i^\vartheta) \leq 1$, the bacteria-free equilibrium F_{i0}^ϑ is the unique equilibrium of Model (1.1).*
2. *When $r(H_i^\vartheta) > 1$, in addition to F_{i0}^ϑ , Model (1.1) has a unique equilibrium $\bar{F}_i^\vartheta > 0$ such that*

$$\bar{F}_i^\vartheta(x) = \left(\frac{(r(H_i^\vartheta))^{\frac{1}{\kappa}} - 1}{\int_{\mathbb{R}} \frac{\phi}{\sqrt{p_i \xi_i^\vartheta}} dy} \right) \frac{\phi(x)}{\sqrt{p_i(x) \xi_i^\vartheta(x)}}.$$

Furthermore, the semi-flow $\{v(\tau, b_{i0}^\vartheta)\}_\tau$ is uniformly persistent, that is, there exists a constant η such that for any $b_{i0}^\vartheta \in L_+^1(\mathbb{R}) \setminus \{0\}$, the unique solution $v(\tau, b_{i0}^\vartheta) = b_i^\vartheta(\tau, \cdot)$ of Model (1.1) with initial data b_{i0}^ϑ satisfies $\liminf_{\tau \rightarrow \infty} \|b_i^\vartheta(\tau, \cdot)\|_{L^1} > \eta$.

3. *The bacteria-free equilibrium F_{i0}^ϑ of Model (1.1) is asymptotically stable if $r(H_i^\vartheta) < 1$ and unstable if $r(H_i^\vartheta) > 1$.*
4. *When $r(H_i^\vartheta) < 1$, the bacteria-free equilibrium F_{i0}^ϑ is globally asymptotically stable in $L_+^1(\mathbb{R})$, that is, for any solution $b_i^\vartheta(\tau, \cdot)$ with initial $b_{i0}^\vartheta \in L_+^1(\mathbb{R}) \setminus \{0\}$, we have $b_i^\vartheta(\tau, \cdot) \rightarrow 0$ in $L_+^1(\mathbb{R})$, as $\tau \rightarrow \infty$.*

We refer to Appendices F-I in [17] for the detailed proof of the above theorem.

Moreover, the profile of the endemic equilibrium \bar{F}_i^ϑ with respect to $x \in \mathbb{R}$ has been described in [16] when the mutation kernel J depends on a small positive parameter (let say $\varepsilon \ll 1$) with the scaling form

$$J_\varepsilon(x) = \varepsilon^{-1} J(\varepsilon^{-1}x). \quad (2.3)$$

More precisely, when $\varepsilon > 0$ is small, then the endemic equilibrium \bar{F}_i^ϑ concentrates on the set \mathcal{S}_i^ϑ defined by

$$\mathcal{S}_i^\vartheta = \left\{ x \in \mathbb{R} : \mathcal{N}_{i0}^\vartheta(x) = \|\mathcal{N}_{i0}^\vartheta\|_\infty \right\}.$$

The set \mathcal{S}_i^ϑ is referred to as the set of Evolutionary Attractors of the within-hots model in the classical adaptive dynamics theory (eg., [22, 38]). Furthermore, when the function $\mathcal{N}_{i0}^\vartheta$ is at least of class \mathcal{C}^1 , with a finite number of maximum, it is shown in [16] that the spectral radius $r(H_{i,\varepsilon}^\vartheta)$ of the operator $H_{i,\varepsilon}^\vartheta$ defined by (2.2) –by replacing the kernel J by J_ε – satisfied, for ε sufficiently small

$$r(H_{i,\varepsilon}^\vartheta) = \max_{x \in \mathbb{R}} \left(\mathcal{N}_{i0}^\vartheta(x) \right)^2 + \mathcal{O}(\varepsilon^2).$$

At the between-host scale, using the next-generation operator approach (eg., [14, 28]), the basic reproduction number $\mathcal{R}_0^i(x)$ of an infected individual of a group i , with resistance level x , is given by

$$\mathcal{R}_0^i(x) = \int_{\mathbb{R}} K(x-y) \bar{\mathcal{R}}_0^i(y) dy,$$

where

$$\overline{\mathcal{R}}_0^i(x) = \frac{\Lambda_i}{\mu_h} \sum_{k \in \mathcal{I}} \chi_k(x),$$

and

$$\chi_k(x) = \int_0^\infty \langle \beta_k(b_k(\tau, x)), \mathbf{\Pi}_k(\tau, 0, x) \mathbf{p}_k(x) \rangle d\tau.$$

The quantity $\chi_k(x)$ is the infectiousness of individuals with an immune system of level k , and a resistance level x to the antimicrobial. Moreover, $\mathbf{\Pi}_i(a, b, x)$, $0 \leq b \leq a < \infty$, is the evolutionary system generated by the linear operator $\Phi_i(\tau, x) = \omega(\tau, x) - \alpha_i(b_i(\tau, x)) - \mu_h$, with $\mathbf{p}_i(x) = (p_i^T(x), p_i^U(x))$, $\alpha_i(b_i(\tau, x)) = \text{diag}(\alpha_i^T(b_i^T(\tau, x)), \alpha_i^U(b_i^U(\tau, x)))$, $\beta_i(b_i(\tau, x)) = (\beta_i^T(b_i^T(\tau, x)), \beta_i^U(b_i^U(\tau, x)))$, and

$$\omega(\tau, x) = \begin{pmatrix} -\omega_U^T(\tau, x) & \omega_T^U(\tau, x) \\ \omega_U^T(\tau, x) & -\omega_T^U(\tau, x) \end{pmatrix}.$$

Next, the existence of a positive equilibrium of Model (1.1)-(1.3) is strongly related to the spectral properties of the linear operator \widehat{M} define by

$$\widehat{M}[\varphi] : L^1(\mathbb{R}) \ni \varphi(\cdot) \mapsto \int_{\mathbb{R}} K(\cdot - y) \overline{\mathcal{R}}_0(y) \varphi(y) dy \in L^1(\mathbb{R}),$$

where

$$\overline{\mathcal{R}}_0(x) = \sum_{k \in \mathcal{I}} \frac{\Lambda_k}{\mu_h} \chi_k(x). \quad (2.4)$$

In addition to the disease-free equilibrium –the DFE– $\mathbf{E}^0 = (\mathbf{S}^0, \mathbf{0}_{L^1((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})})$, with $\mathbf{S}^0 = (\Lambda_i / \mu_h)_{i \in \mathcal{I}}$, which is always an equilibrium of Model (1.2)-(1.3), this model also exhibits an endemic equilibrium given by the following result

Theorem 2.6 *Let Assumptions 2.2 and 2.1 hold. If the spectral radius $r(\widehat{M})$ of \widehat{M} is such that $r(\widehat{M}) > 1$, then system (1.2)-(1.3) has a unique endemic equilibrium $\mathbf{E}^* = (\mathbf{S}^*, \mathbf{I}^*(\tau, x))$, such that $\forall i \in \mathcal{I}$,*

$$S_i^* = \frac{S_i^0}{r(\widehat{M})} \quad \text{and} \quad \mathbf{I}_i^*(\tau, x) = \mu_h (r(\widehat{M}) - 1) \phi_{\widehat{M}}^*(x) S_i^* \mathbf{\Pi}_i(\tau, 0, x) \mathbf{p}_i(x),$$

where $\phi_{\widehat{M}}^*$ is principal eigenfunction of \widehat{M} , associated to $r(\widehat{M})$ and normalized such that $\|\phi_{\widehat{M}}^*\|_{L^1} = 1$.

Therefore, the threshold dynamics of Model (1.2)-(1.3) is summarize as follows

Theorem 2.7 *Let Assumptions 2.2 and 2.1 hold. Then,*

- (i) *If $r(\widehat{M}) < 1$ or $\sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(b_{i,0}(\tau, x)), \mathbf{I}_{i,0}(\tau, x) \rangle d\tau = 0$, then the disease-free equilibrium $\mathbf{E}^0 = (\mathbf{S}^0, \mathbf{0}_{L^1((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})})^t$ of system (1.2)-(1.3) is globally asymptotically stable in the sens that*

$$\lim_{t \rightarrow \infty} (S_i(t), I_i^T(t, \cdot, \cdot), I_i^U(t, \cdot, \cdot))_{i \in \mathcal{I}} = \mathbf{E}^0,$$

where the above convergence holds for the topology of $\mathbb{R}^n \times L^1((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})$. Moreover, the disease-free equilibrium \mathbf{E}^0 becomes unstable whenever $r(\widehat{M}) > 1$.

- (ii) *If $r(\widehat{M}) > 1$ and $\sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(b_{i,0}(\tau, x)), \mathbf{I}_{i,0}(\tau, x) \rangle d\tau > 0$, then the semiflow $\{\Psi(t, \cdot)\}_{t \geq 0}$ generated by system (1.2)-(1.3) is uniformly persistent in the sens that, there exists a constant $\eta > 0$ such that*

$$\liminf_{t \rightarrow \infty} \| (I_i^T(t, \cdot, \cdot), I_i^U(t, \cdot, \cdot))_{i \in \mathcal{I}} \|_{L^1_+} \geq \eta.$$

The above result describes the asymptotic behaviour of Model (1.2)-(1.3) for any given probability density function K . However, we can go further in our analysis when the probability kernel K is highly concentrated with the scaling form

$$K_\xi(x) = \xi^{-1}K(\xi^{-1}x). \quad (2.5)$$

Furthermore, we shall make use of the following assumption

Assumption 2.8 *We assume that, the kernel K is symmetric, the function $\bar{\mathcal{R}}_0$ defined by (2.4) is at least of class \mathcal{C}^2 , satisfies $\bar{\mathcal{R}}_0(x) \rightarrow 0$ as $|x| \rightarrow \infty$, and the set*

$$\mathcal{N} = \{x \in \mathbb{R} : \bar{\mathcal{R}}_0(x) = \|\bar{\mathcal{R}}_0\|_\infty\} \neq \emptyset.$$

Similarly to the within-host scale where sets \mathcal{S}_s are introduced, note that the set \mathcal{N} is referred to as the set of Evolutionary Attractors of the between-hosts model.

Denoting by \widehat{M}_ξ , the operator \widehat{M} where the kernel K is replaced by K_ξ , it follows from [16] that the spectral radius $r(\widehat{M}_\xi)$ of the operator \widehat{M}_ξ have an asymptotic expansion of the form

$$\frac{r(\widehat{M}_\xi)}{\|\bar{\mathcal{R}}_0\|_\infty} = 1 + \zeta_1[x]\xi + \zeta_2[x]\xi^2 + \mathcal{O}(\xi^3), \quad \text{for all } x \in \mathcal{N},$$

where $\zeta_1[x] = -\sqrt{-\frac{\bar{\mathcal{R}}_0''(x)}{2\|\bar{\mathcal{R}}_0\|_\infty}}$ while $\zeta_2[x]$ depends on the successive derivatives $\bar{\mathcal{R}}_0^{(l)}(x)$, $l \geq 2$.

Moreover, the principal eigenfunction $\phi_{\widehat{M}_\xi}^*$, associated with $r(\widehat{M}_\xi)$, exhibits a concentration phenomenon in the set of resistance levels. More precisely, let us define $x^* \in \mathcal{N}$ the unique point of \mathcal{N} such that, for each other point $x \in \mathcal{N}$, we have $(\zeta_j[x^*])_j > (\zeta_j[x])_j$. Such a relation is written in the sense of a lexicographical order, that is, either $\zeta_1[x^*] > \zeta_1[x]$, or $(\zeta_1[x^*] = \zeta_1[x]; \zeta_2[x^*] > \zeta_2[x])$, and so on. We then have (see [16]), for all $\nu > 0$

$$\int_{\mathbb{R} \setminus B(x^*, \nu)} \phi_{\widehat{M}_\xi}^* dx = C(\nu, \xi) \text{ with } C(\nu, \xi) = \mathcal{O}(\xi^\infty) \text{ as } \xi \rightarrow 0,$$

and for each continuous and bounded function $f \in \mathcal{C}_b^0(\mathbb{R})$ one has

$$\lim_{\xi \rightarrow 0} \int_{\mathbb{R}} \phi_{\widehat{M}_\xi}^* f dx = f(x^*).$$

In particular, the unique endemic equilibrium $\mathbf{E}_\xi^* = (\mathbf{S}_\xi^*, \mathbf{I}_\xi^*(\tau, x))$ at the within-host scale dynamics, when $K \equiv K_\xi$, is such that,

$$\lim_{\xi \rightarrow 0} \int_{\mathbb{R}} \mathbf{I}_{i,\xi}^*(\cdot, x) dx = (\|\bar{\mathcal{R}}_0\|_\infty - 1) \frac{\mu_h S_i^0}{\|\bar{\mathcal{R}}_0\|_\infty} \mathbf{\Pi}_i(\cdot, 0, x^*) \mathbf{p}_i(x^*), \quad \forall i \in \mathcal{I}.$$

3 Model's typical dynamics and discussion

We illustrate an example of typical dynamics that can be simulated by the nested model (1.1)-(1.3). The model simultaneously captures the outbreak dynamics as well as the evolutionary dynamics of the average resistance level within the host population. The within-host model parameters are basically the same as in [17]. Intuitively there exist two threshold levels, assumed here 0 and 1 (called reference "sensitive" and "resistant" strains) such that, a strain with resistance level x can be classically referred to as "sensitive", "intermediate", or "resistant" depending on whether $x < 0$, $0 < x < 1$, or $x > 1$. For sake of simplicity, we assume that the host population is homogeneous in terms of immune system level, *i.e.*, $\text{card}(\mathcal{I}) = 1$. For all illustrative scenarios, we will assume that the disease is persistent in the host population, *i.e.*, the $\|\bar{\mathcal{R}}_0\|_\infty > 1$. The probability density functions at the within-host scale ($J \equiv J_\xi$) and the between-host scale ($K \equiv K_\xi$) are assumed of type (2.3) and (2.5) respectively.

Within-host parameterization. The antimicrobial killing rate function $k(\cdot)$ is a decreasing function with respect to the resistance level x such that, $k(x) = k_0 \left(\frac{k_1}{k_0}\right)^x$, where k_0 and k_1 are the antimicrobial activity undergone by the reference sensitive and resistant strains. Moreover, knowing p_0 and p_1 , respectively the intrinsic growth rate of reference strains 0 and 1, a suitable expression for function of p is $p(x) = p_m \left[1 + \left(\frac{p_m - p_0}{p_0}\right) \left(\frac{p_0}{p_1} \cdot \frac{p_m - p_1}{p_m - p_0}\right)^x\right]^{-1}$, where p_m is the upper bound of the intrinsic growth rate p and $0 < p_1 < p_0 < p_m$. The qualitative behaviour of functions k and p can be found in ([17], Figure 2).

Between-host parameterization. Transmission rates β^ϑ s and disease-induced mortality rates α^ϑ are assume of the form (1.4). The rate at which infected individuals are treated $p^T(\cdot)$ is assumed to be a decreasing function with respect to the resistance level x . The main idea behind such an assumption is that the probability of treating an infection with a given antimicrobial diminishes when the resistance to this antimicrobial increases. By setting p_{max} as the maximum treatment rate allowed in the host population, the function p^T is defined such that $p^T(-1) = 0.99 \times p_{max}$, and $p^T(1) = 0.5 \times p_{max}$. That is,

$$p^T(x) = \frac{p_{max}}{1 + (1/99) \times 99^{(x+1)/2}}.$$

Next, let ω_{max} be the maximum influx rate between treated (I^T) and untreated (I^U) states in the whole population. We assume that the rate at which infected individuals stop the treatment with a given antimicrobial increases with the resistance level such that $\omega_U^T(-1) = 10^{-3} \times \omega_{max}$ and $\omega_U^T(1) = 0.99 \times \omega_{max}$. That is, individuals with low resistance levels ($x \approx -1$) will mainly stay in the treatment regimen, while those with higher resistance levels ($x \approx 1$) will leave the treatment with a higher rate such that, $\omega_U^T(x) = \omega_{max} \times f_U^T(x)$, with $f_U^T(x) = [1 + 99^{-(x+1)/2} \times 999^{-(x-1)/2}]^{-1}$. Finally, the rate at which untreated infections become treated is such that $\omega_T^U(x) = \omega_{max} \times (1 - f_U^T(x))$.

Initial conditions and model outputs. The initial bacterial population $b_0^\vartheta(x)$ is assumed to be composed by a sensitive bacterial population with average resistance level $x = 0$. Hence, we set $b_0^\vartheta(x) = m_0 \times \mathcal{N}(0, \sigma_0, x)$, where $\mathcal{N}(0, \sigma_0, x)$ stands for the normalized density function of the Gaussian distribution at x with mean 0 and variance σ_0^2 . This means that the initial bacterial population is mostly composed of the reference "sensitive" strain. At the between-hots scale, the initial condition of the epidemiological model is taken randomly.

Moreover, the within-host model (1.1) allows to follow evolutionary parameters such as the average level of resistance for treated (η^T) and untreated (η^U) bacteria. For individuals infected since time τ , this reads as $\eta^T(\tau) = \int_{\mathbb{R}} x \frac{b^T(\tau, x)}{B^T(\tau)} dx$, and $\eta^U(\tau) = \int_{\mathbb{R}} x \frac{b^U(\tau, x)}{B^U(\tau)} dx$. At the between-host level, Model (1.2)-(1.3), the average level of resistance ($\eta(t)$) of the host population at time t is such that

$$\eta(t) = \int_{\mathbb{R}} x \frac{\int_0^\infty I^T(t, \tau, x) d\tau + \int_0^\infty I^U(t, \tau, x) d\tau}{I(t)} dx,$$

where $I(t) = \int_0^\infty \int_{\mathbb{R}} (I^T(t, \tau, x) + I^U(t, \tau, x)) dx d\tau$. Two simulated scenario are then considered, the first when the treatment is successful at the within-host level, and the second when the treatment failed at the within-hots level.

Simulated scenarios. For all our simulated scenarios, the infection is assumed here to be always unsuccessful for untreated individuals, *ie.*, the immune system alone is no more enough to control the infection such that $\max_{x \in \mathbb{R}} \mathcal{N}_0^U(x) > 1$, leading to the bacterial persistence for untreated infections.

Our first scenario is for the case where the treatment is successful at the within-host level, *ie.*, $\max_{x \in \mathbb{R}} \mathcal{N}_0^T(x) < 1$ (Figure 2C). In such a situation, the bacterial load is under control in the relatively short term (Figure 2A). The average proportion of treated infections in the host population has a

moderate impact on the average level of resistance in this population. Indeed, increasing the value of p_{\max} has a marginal effect on the evolutionary dynamics of the resistance level η (Figure 2D), and the average resistance of the bacterial population is not higher compared to the one of the initial bacterial population (Figure 2D). Because the epidemic is persistent at the between-host level, *ie.* $\mathcal{R}_0 > 1$, the outbreak will be not under control whatever the treatment rate of the host population (Figure 2G,H,I). However, the prevalence of the infection can be very small for some duration. Such a period during which the outbreak remains under control strongly increases with the treatment rate of the host population (Figure 2G,H,I).

In the second scenario, the treatment is assumed unsuccessful at the within-host level, *ie.*, $\max_{x \in \mathbb{R}} \mathcal{N}_0^T(x) > 1$ (Figure 3C). In such a situation, the bacterial load also remains persistent for treated infections (Figure 3A). In contrast to the treatment success scenario (Figure 2), the average proportion of treated infections in the host population strongly impacts the average level of resistance in this population. Indeed, increasing the value of p_{\max} has a strong effect on the evolutionary dynamics of the resistance level η (Figure 3D), and the average resistance of the bacterial population becomes much higher compared to the one of the initial bacterial population (Figure 3D). Such an increase in the bacterial resistance level in the host population strongly increases with the treatment rate of this population (Figure 3D). Similarly to the previous scenario, the epidemic is persistent at the between-host level because $\mathcal{R}_0 > 1$, and so the outbreak will be not under control whatever the treatment rate of the host population, but the prevalence of the infection can be very small for some duration (Figure 3G,H,I). However, compared to the situation where the treatment is a success at the within-host scale (Figure 2G,H,I), the frequency at which the host population is treated has a marginal effect of such a period during which the outbreak remains under control (Figure 3G,H,I).

Optimizing the treatment rate in the host population is key to controlling both the epidemic outbreak and the average level of resistance. Increasing the treatment rate in the host population contributes to reducing the epidemic size at the between-host scale whatever the treatment outcome at the within-host scale (Figures 2G,H,I and 3G,H,I). This is mainly explained by the fact that, even in the scenario of treatment failure, the within-host infection is under control for some period (Figure 3A), but the second phase begins with an increase in the bacterial population density (Figure 3A). In contrast, increasing the treatment rate in the host population strongly increases the bacterial resistance level in the case of treatment failure (Figure 3D), compared to the case of treatment success (Figure 2D) where the level of resistance remains very similar to the one of the initial bacterial population. Therefore, depending on the treatment regimen introduced in the host population, it becomes necessary and interesting to determine an optimal treatment rate for this population to control both the outbreak as well as the average level of antimicrobial resistance.

Transitions between infected populations (treated and untreated) can impact the average level of resistance. Assume the scenario where the treatment is successful at the within-host scale (Figure 2A), and a high proportion of infected individuals is under treatment, $p_{max} = 0.9$. While the transition rates of the infected individuals between treated and untreated status have a marginal impact on the host population’s epidemiological dynamics (Figure 4D,E,F), the situation is quite contrasting with the evolutionary dynamics of the average resistance level (Figure 4A). Indeed, even in the case of treatment success at the within-host scale, increasing the rate at which the host population can move from a treated infection to an untreated infection, and vice-versa, contributes to having a much higher average resistance level in the host population compared to the initial resistance level (Figure 4D).

Nested models parameterization issue. Explicitly connecting the within- to and between-host scales are crucial to gain a more realistic picture aiming to integrate into the same modelling framework the epidemic dynamics and the evolutionary dynamics of antimicrobial resistance. However, such an approach requires making assumptions about the parameters at the within-host scale that are equally unknown as the parameters at the between-host scale and hence leading to uncertainty about the appropriate

parametrization [44]. Such uncertainty is amplified by our approach where the level of resistance is considered a continuous quantitative trait, compared to the classical qualitative (or "binary") approaches [17].

Time-scale separation hypothesis. Within the context of nesting within- and between-host scales, for the modelling of the epidemiology and evolution of pathogens, some studies assumed that the epidemiological and evolutionary time scales are distinct, *ie.*, the within-host dynamic is fast relative to the between-host dynamic such that the within-host model remains at equilibrium, *eg.* [2, 3, 7, 11, 23, 47]. Although such an assumption on the within-host equilibrium dynamic' might be appropriate for chronic infections, it leads to a population-scale model that does not explicitly account for the individual time-dependent infectiousness dynamics [26]. Furthermore, our illustrative examples (Figures 2,3) strongly highlight the infectiousness' time-dependency of infected individuals and show that the within-host dynamic is not necessarily faster compared to the within-host dynamic.

4 Preliminaries and technical materials

We will go through details on the proof of our main results, namely Theorem 2.7. We will first discuss the existence of a positive global solution of the nested model. Next, we will give details on the derivation of the basic reproduction number of System (1.2)-(1.3) for individuals with an immune system of level i and resistance level x . We will also derive the existence of a unique endemic equilibrium of System (1.2)-(1.3) when $r(\widehat{M}) > 1$, as well as the long-term persistence of the epidemic in such a case.

4.1 Existence of the semiflow

By setting $\mathbf{S}(t) = (S_i(t))_{i \in \mathcal{I}}$, $\mathbf{I}_i(t, \tau, x) = (I_i^T(t, \tau, x), I_i^U(t, \tau, x))$ and $\mathbf{I}(t, \tau, x) = (\mathbf{I}_i(t, \tau, x))_{i \in \mathcal{I}}$, it is useful to write System (1.2)-(1.3) into a compact form. That is,

$$\begin{cases} \dot{\mathbf{S}}(t) = \mathbf{\Lambda} - \mathbf{S}(t) \int_{\mathbb{R}} \lambda(t, x) dx - \mu_h \mathbf{S}(t), \\ \mathbf{I}(t, \tau = 0, x) = \lambda(t, x) \text{diag}(\mathbf{S}(t)) \mathbf{p}(x), \\ (\partial_t + \partial_\tau) \mathbf{I}(t, \tau, x) = \text{diag}(\mathbf{\Phi}(\tau, x)) \mathbf{I}(t, \tau, x), \end{cases} \quad (4.1)$$

where $\lambda(t, x) = \int_{\mathbb{R}} K(x - y) \sum_i \int_0^\infty \langle \beta_i(b_i(\tau, y)), \mathbf{I}_i(t, \tau, y) \rangle d\tau dy$, $\mathbf{\Lambda} = (\Lambda_i)_{i \in \mathcal{I}}$, $\mathbf{p}(x) = (\mathbf{p}_i(x))_{i \in \mathcal{I}}$, and $\mathbf{\Phi}(\tau, x) = (\mathbf{\Phi}_i(\tau, x))_{i \in \mathcal{I}}$.

Next, we establish the existence of a positive global solution of the system (4.1). We first formulate system (4.1) in an abstract Cauchy problem. For that, we introduce the Banach space $\mathcal{X} = \mathbb{R}^n \times L^1(\mathbb{R}, \mathbb{R}^{2n}) \times L^1((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})$, endowed with the usual product norm $\|\cdot\|_{\mathcal{X}}$ as well as its positive cone \mathcal{X}_+ . Let $A : D(A) \subset \mathcal{X} \rightarrow \mathcal{X}$ be the linear operator defined by $D(A) = \mathbb{R}^n \times \{\mathbf{0}_{L^1}\} \times W^{1,1}((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})$ and

$$A(\mathbf{S}, \mathbf{0}_{L^1}, \mathbf{I}) = \left(-\mu_h \mathbf{S}, -\mathbf{I}(0, x), -\partial_\tau \mathbf{I} + \text{diag}(\mathbf{\Phi}(\tau, x)) \mathbf{I} \right). \quad (4.2)$$

Let us introduce the non-linear map $F : \overline{D(A)} \rightarrow \mathcal{X}$ defined by

$$F(\mathbf{S}, \mathbf{0}_{L^1}, \mathbf{I}) = \left(\mathbf{\Lambda} - \mathbf{S}(t) \int_{\mathbb{R}} \lambda(t, x) dx, \lambda(t, x) \text{diag}(\mathbf{S}(t)) \mathbf{p}(x), \mathbf{0}_{L^1((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})} \right).$$

By identifying $\varphi(t)$ together with $(\mathbf{S}(t), \mathbf{0}_{L^1}, \mathbf{I}(t, \cdot, \cdot))^t$ and by setting $\varphi_0 = (\mathbf{S}_0, \mathbf{0}_{L^1}, \mathbf{I}_0(\cdot, \cdot))^t$ the associated initial condition, System (4.1) becomes

$$\begin{cases} \frac{d\varphi(t)}{dt} = A\varphi(t) + F(\varphi(t)), \\ \varphi(0) = \varphi_0. \end{cases} \quad (4.3)$$

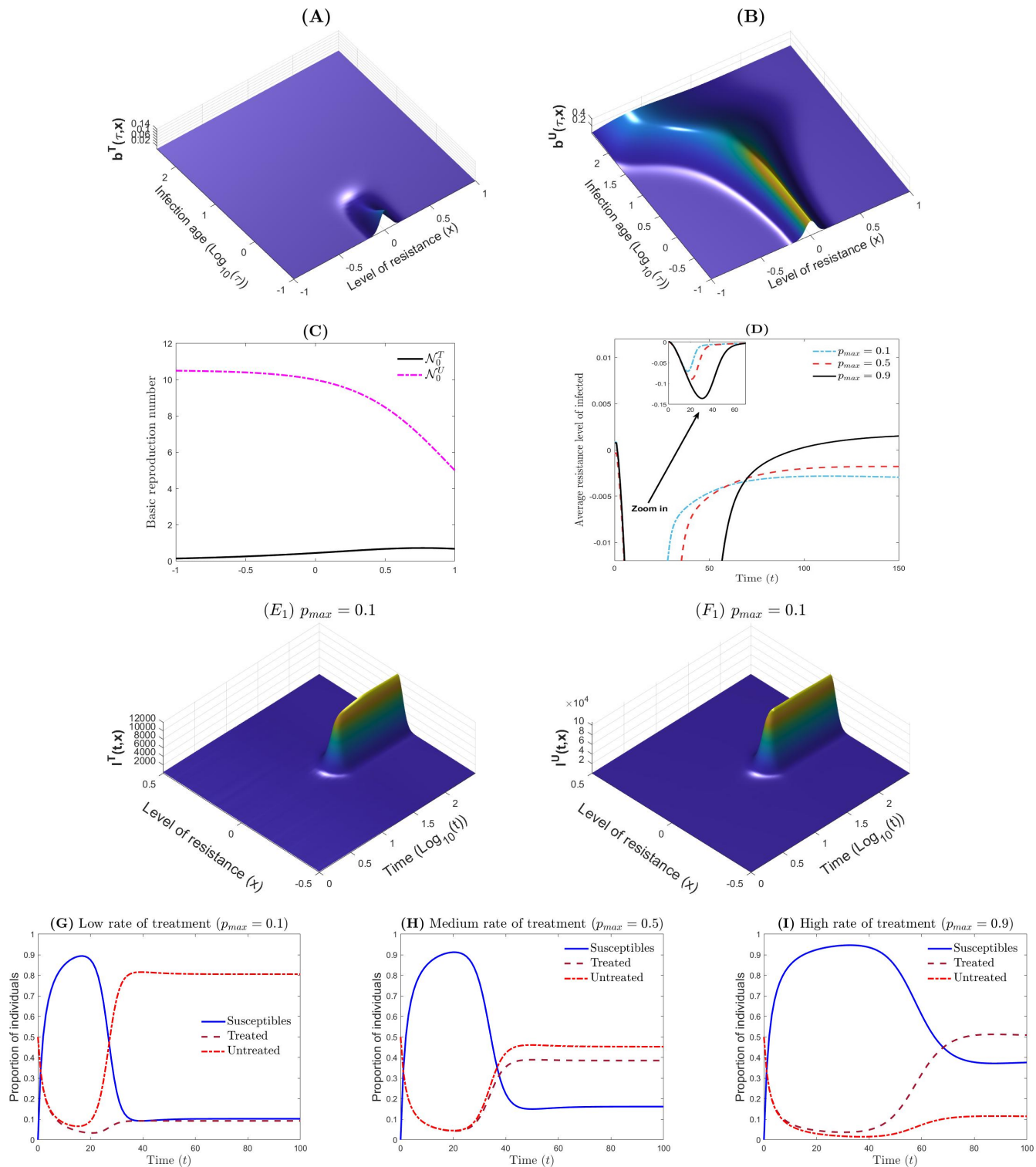


Figure 2: Dynamics of the nested model when the therapeutic treatment is successful. **(A,B)** Distribution of the bacterial population (treated and untreated) with respect to time τ and resistance level x . **(C)** The basic reproduction numbers at the within-host level $\mathcal{N}_0^T(x)$ and $\mathcal{N}_0^U(x)$, with and without drug respectively. **(D)** Time evolution of the average resistance level $\eta(t)$ of the host population. **(E,F)** Distribution of the infectious individuals (treated and untreated) with respect to time t and resistance level x . **(G,H,I)** Time evolution of the proportion of individuals with respect to the treatment rate. Parameter values are $(\sigma_0, m_0, k_0, p_1/p_0, k_1/k_0) = (0.05, 0.05, 20, 0.5, 0.3)$ and $\Lambda = 5e4$, $\mu_h = 5.2675e - 2$, $\beta_0 = 1.848e - 3$, $\alpha_0 = 7.5e - 2$, $\omega_{max} = 1e - 3$, $r_0 = 9e2$.

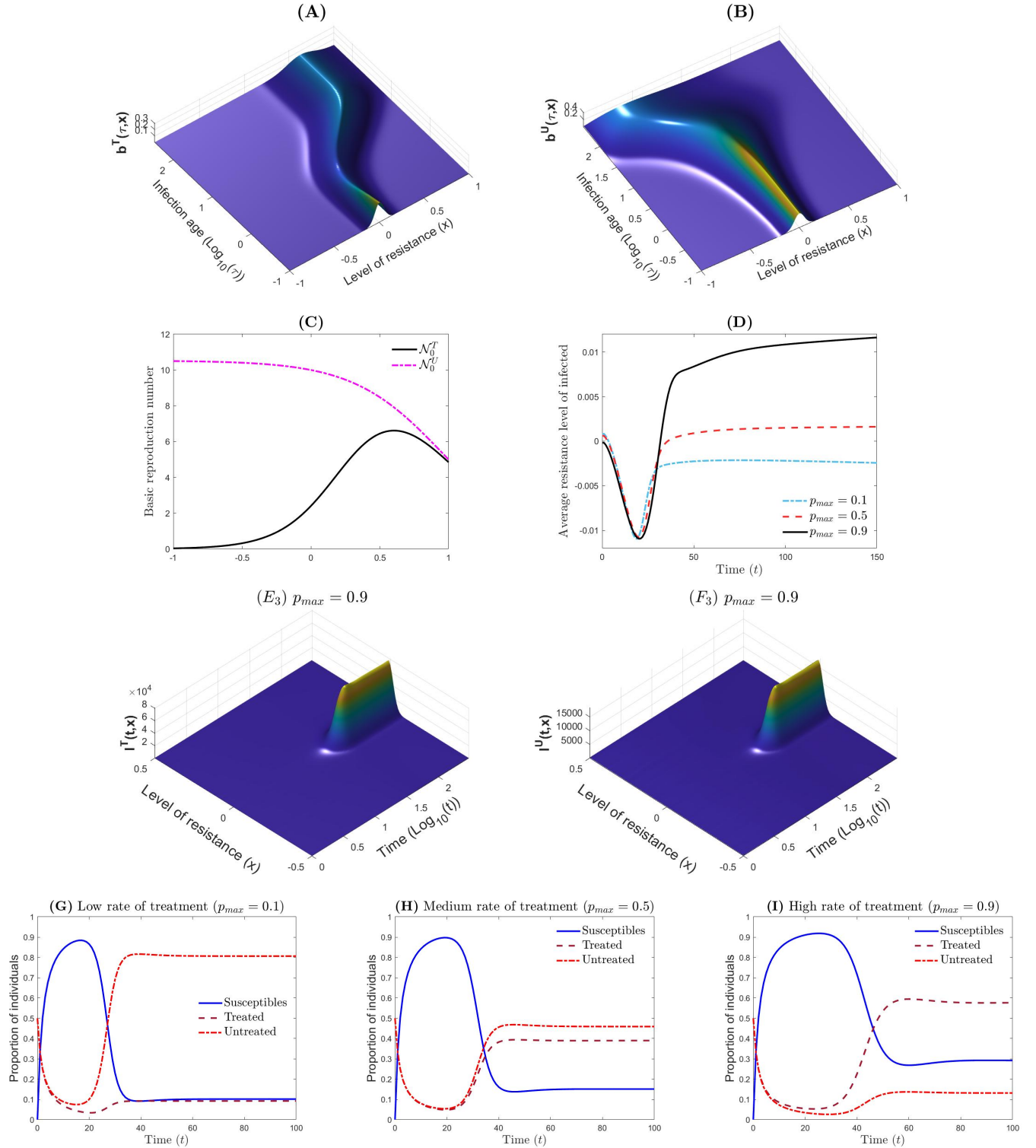


Figure 3: Dynamics of the nested model when the therapeutic treatment failed. **(A,B)** Distribution of the bacterial population (treated and untreated) with respect to time τ and resistance level x . **(C)** The basic reproduction numbers at the within-host level $\mathcal{N}_0^T(x)$ and $\mathcal{N}_0^U(x)$, with and without drug respectively. **(D)** Time evolution of the average resistance level $\eta(t)$ of the host population. **(E,F)** Distribution of the infectious individuals (treated and untreated) with respect to time t and resistance level x . **(G,H,I)** Time evolution of the proportion of individuals with respect to the treatment rate. Parameter values are $(\sigma_0, m_0, k_0, p_1/p_0, k_1/k_0) = (0.05, 0.05, 3, 0.5, 0.01)$ and $\Lambda = 5e4$, $\mu_h = 5.2675e - 2$, $\beta_0 = 1.848e - 3$, $\alpha_0 = 7.5e - 2$, $\omega_{max} = 1e - 3$, $r_0 = 9e2$.

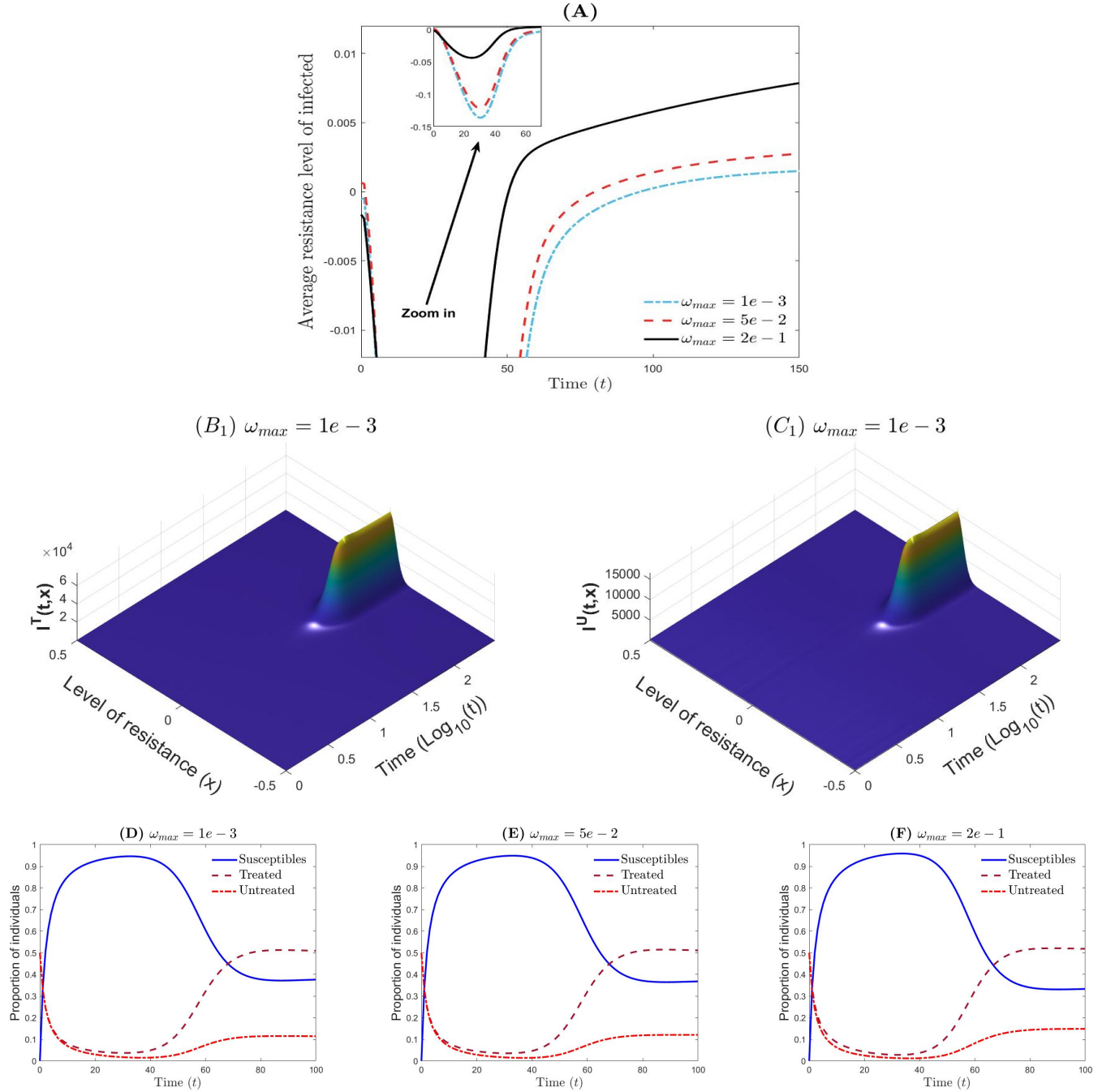


Figure 4: Dynamics of the nested model when the therapeutic treatment is successful and the maximum treatment rate p_{max} is high. (A) Time evolution of the average resistance level $\eta(t)$ of the host population. (B,C) Distribution of the infectious individuals (treated and untreated) with respect to time t and resistance level x . (D,E,F) Time evolution of the proportion of individuals with respect to the maximum rate at which individuals are leaving the treatment. Parameter values are $(\sigma_0, m_0, k_0, p_1/p_0, k_1/k_0) = (0.05, 0.05, 20, 0.5, 0.3)$ and $\Lambda = 5e4$, $\mu_h = 5.2675e-2$, $\beta_0 = 1.848e-3$, $\alpha_0 = 7.5e-2$, $p_{max} = 0.9$, $r_0 = 9e2$.

By setting $\mathcal{X}_0 = D(A)$ and $\mathcal{X}_{0+} = \mathcal{X}_0 \cap \mathcal{X}_+$, the positivity and boundedness of the solutions of System (4.1) are provided by the following result.

Theorem 4.1 *There exists a unique strongly continuous semiflow $\{\Psi(t, \cdot) : \mathcal{X}_0 \rightarrow \mathcal{X}_0\}_{t \geq 0}$ such that, for each $\varphi_0 \in \mathcal{X}_{0+}$, the map $\varphi \in \mathcal{C}([0, \infty), \mathcal{X}_{0+})$ defined by $\varphi = \Psi(\cdot, \varphi_0)$ is a mild solution of (4.3). That is, $\int_0^t \varphi(s) ds \in D(A)$ and $\varphi(t) = \varphi_0 + A \int_0^t \varphi(s) ds + \int_0^t F(\varphi(s)) ds$ for all $t \geq 0$. Moreover, $\{\Psi(t, \cdot)\}_t$ satisfies the following properties:*

1. Let $\Psi(t, \varphi_0) = (S(t), \mathbf{0}_{L^1}, \mathbf{I}(t, \cdot, \cdot))^t$, then the following Volterra formulation holds true for all $i \in \mathcal{I}$

$$I_i(t, \tau, x) = \begin{cases} \Pi_i(\tau, \tau - t, x) I_{i0}(\tau - t, x), & \text{if } t \leq \tau, \\ \Pi_i(\tau, 0, x) \mathbf{p}_i(x) \lambda(t - \tau, x) S_i(t - \tau), & \text{if } t > \tau, \end{cases} \quad (4.4)$$

coupled with the $S_i(t)$ equation of (4.1).

2. For all $\varphi_0 \in \mathcal{X}_{0+}$, and for all $t \geq 0$, one has

$$\sum_{i \in \mathcal{I}} \left(S_i(t) + \int_{\mathbb{R}} \int_0^\infty \left(I_i^T(t, \tau, x) + I_i^U(t, \tau, x) \right) d\tau dx \right) \leq \max \left\{ \frac{\bar{\Lambda}}{\mu_h}, \sum_{i \in \mathcal{I}} \left(S_{i0} + \int_{\mathbb{R}} \int_0^\infty \left(I_{i0}^T(\tau, x) + I_{i0}^U(\tau, x) \right) d\tau dx \right) \right\} \quad (4.5)$$

where $\bar{\Lambda} = \sum_{i \in \mathcal{I}} \Lambda_i$. Furthermore, the subset of the phase space

$$\Gamma = \left\{ (S, \mathbf{I}) \in \mathbb{R}^n \times L^1((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n}) \mid \sum_{i \in \mathcal{I}} \left(S_i(t) + \int_{\mathbb{R}} \int_0^\infty \left(I_i^T(t, \tau, x) + I_i^U(t, \tau, x) \right) d\tau dx \right) \leq \frac{\bar{\Lambda}}{\mu_h} \right\},$$

is positively invariant and attracts all nonnegative solutions.

3. The semiflow $\{\Psi(t, \cdot)\}_t$ generated by (4.1) is bounded dissipative, that is, there exists a bounded set $\mathcal{B} \subset \mathcal{X}_0$ such that for any bounded set $U \subset \mathcal{X}_0$, we can find $\sigma = \sigma(U, \mathcal{B}) \geq 0$ such that $\Psi(t, U) \subset \mathcal{B}$ for $t \geq \sigma$.

Proof. It is easy to check that the operator A is a Hille-Yosida operator. Then standard results apply to provide the existence and uniqueness of a mild solution to (4.1) (we refer to [34, 43] for more details). The Volterra formulation is also standard and we refer to [32, 46] for more details.

The S_i equation of (4.1) gives $\dot{S}_i(t) \leq \Lambda_i - \mu_h S_i(t)$, that is

$$S_i(t) \leq \max \left\{ \frac{\Lambda_i}{\mu_h}, S_{i0} \right\}.$$

Next, for estimate (4.5), let $\varphi_0 \in \mathcal{X}_{0+}$, then adding up the S_i 's equation together with the I_i^T 's and I_i^U 's equations of (1.3) yields for all $i \in \mathcal{I}$

$$\frac{d}{dt} \left(S_i(t) + \int_{\mathbb{R}} \int_0^\infty \left(I_i^T(t, \tau, x) + I_i^U(t, \tau, x) \right) d\tau dx \right) \leq \Lambda_i - \mu_h S_i(t) - \mu_h \int_{\mathbb{R}} \int_0^\infty \left(I_i^T(t, \tau, x) + I_i^U(t, \tau, x) \right) d\tau dx.$$

It comes

$$\limsup_{t \rightarrow \infty} \sum_{i \in \mathcal{I}} \left(S_i(t) + \int_{\mathbb{R}} \int_0^\infty \left(I_i^T(t, \tau, x) + I_i^U(t, \tau, x) \right) d\tau dx \right) \leq \frac{\bar{\Lambda}}{\mu_h}.$$

From where one deduces estimate (4.5) and which ends item 2. of the theorem.

The bounded dissipativity of the semiflow $\{\Psi(t, \cdot)\}_t$ is a direct consequence of estimate 2. ■

By using the similar method as in [8] (see Lemma 2.1), the following result is straightforward.

Lemma 4.2 *Denote $\Pi_i(a, b, x) = \left(\Pi_{i,j}^k(a, b, x) \right)_{k,j}$, with $k, j \in \{T, U\}$. For fixed $b \geq 0$, there exists some constants $\gamma_0 > 0$ and $\gamma_1 > 0$ such that*

$$\gamma_0 \leq \Pi_{i,j}^k(a, b, x) \leq \gamma_1 e^{-\mu_h(a-b)} \leq \gamma_1,$$

for all $i \in \mathcal{I}$, $k, j \in \{T, U\}$, $x \in \mathbb{R}$ and $a \geq b$.

4.2 The basic reproduction number

In the absence of infection, that is $\mathbf{I}(t, \tau, x) = \mathbf{0}$, the system (4.1) has a disease-free equilibrium (DFE) given by $\mathbf{E}^0 = (\mathbf{S}^0, \mathbf{0}_{L^1((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})})$, with $\mathbf{S}^0 = (\Lambda_i / \mu_h)_{i \in \mathcal{I}}$. Let $\Theta_i(t, x)$ be the number of new infections in the host population of group i at time t , and with resistance level x . Then in an initially infection-free population, by (4.1), we have

$$\Theta_i(t, x) = \lambda(t, x) S_i^0 = \left(\int_{\mathbb{R}} K(x - y) \sum_{k \in \mathcal{I}} \int_0^\infty \langle \beta_k(b_k(\tau, y)), \mathbf{I}_k(t, \tau, y) \rangle d\tau dy \right) S_i^0,$$

where $\langle \cdot; \cdot \rangle$ is the usual scalar product.

Linearizing the Volterra formulation (4.4) at the DFE, it comes

$$\mathbf{I}_k(t, \tau, x) = \begin{cases} \mathbf{\Pi}_k(\tau, \tau - t, x) \mathbf{I}_{k0}(\tau - t, x), & \text{if } t \leq \tau, \\ \lambda(t - \tau, x) S_k^0 \mathbf{\Pi}_k(\tau, 0, x) \mathbf{p}_k(x), & \text{if } t > \tau. \end{cases}$$

From where,

$$\begin{aligned} \Theta_i(t, x) &= \int_{\mathbb{R}} K(x - y) \left(S_i^0 \sum_{k \in \mathcal{I}} \int_0^t \lambda(t - \tau, y) S_k^0 \langle \beta_k(b_k(\tau, y)), \mathbf{\Pi}_k(\tau, 0, y) \mathbf{p}_k(y) \rangle d\tau \right) dy + f_i(t, x), \quad \forall t \geq 0, \\ &= \int_{\mathbb{R}} K(x - y) \left(S_i^0 \sum_{k \in \mathcal{I}} \int_0^t \langle \beta_k(b_k(\tau, y)), \mathbf{\Pi}_k(\tau, 0, y) \mathbf{p}_k(y) \rangle \Theta_k(t - \tau, y) d\tau \right) dy + f_i(t, x), \quad \forall t \geq 0, \end{aligned}$$

where $f_i(t, x)$ is the number of new infections produced by the initial population. Therefore, the basic reproduction number $\mathcal{R}_0^i(x)$ of individuals of group i is calculated as

$$\mathcal{R}_0^i(x) = \int_{\mathbb{R}} K(x - y) \bar{\mathcal{R}}_0^i(y) dy,$$

where

$$\bar{\mathcal{R}}_0^i(x) = S_i^0 \sum_{k \in \mathcal{I}} \int_0^\infty \langle \beta_k(b_k(\tau, x)), \mathbf{\Pi}_k(\tau, 0, x) \mathbf{p}_k(x) \rangle d\tau = S_i^0 \sum_{k \in \mathcal{I}} \chi(x).$$

4.3 Proof of Theorem 2.6

The equilibrium of system (4.1) is obtained by solving the following system

$$\begin{cases} 0 = \Lambda_i - S_i^* \int_{\mathbb{R}} \lambda^*(z) dz - \mu_h S_i^*, \\ \mathbf{I}_i^*(\tau = 0, x) = \mathbf{p}_i(x) \lambda^*(x) S_i^*, \\ \partial_\tau \mathbf{I}_i^*(\tau, x) = (\boldsymbol{\omega}(\tau, x) - \boldsymbol{\alpha}_i(b_i(\tau, x)) - \mu_h) \mathbf{I}_i^*(\tau, x), \end{cases} \quad (4.6)$$

where

$$\lambda^*(x) = \int_{\mathbb{R}} K(x - y) \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(b_i(\tau, y)), \mathbf{I}_i^*(\tau, y) \rangle d\tau dy. \quad (4.7)$$

Solving (4.6) for S_i^* and \mathbf{I}_i^* yields

$$S_i^* = \frac{\Lambda_i}{\mu_h + \int_{\mathbb{R}} \lambda^*(z) dz} \quad (4.8)$$

and

$$\mathbf{I}_i^*(\tau, x) = \lambda^*(x) S_i^* \mathbf{\Pi}_i(\tau, 0, x) \mathbf{p}_i(x). \quad (4.9)$$

Replacing (4.9) and (4.8) in (4.7) leads to

$$\left(1 + \mu_h^{-1} \int_{\mathbb{R}} \lambda^*(z) dz\right) \lambda^*(x) = \int_{\mathbb{R}} K(x-y) \overline{\mathcal{R}}_0(y) \lambda^*(y) dy,$$

where $\overline{\mathcal{R}}_0$ is given by (2.4).

The above equality rewrites

$$\widehat{M}[\lambda^*](x) = \left(1 + \mu_h^{-1} \int_{\mathbb{R}} \lambda^*(z) dz\right) \lambda^*(x), \quad (4.10)$$

where \widehat{M} is the operator defined by

$$\widehat{M}[\varphi] : L^1(\mathbb{R}) \ni \varphi(\cdot) \mapsto \int_{\mathbb{R}} K(\cdot - y) \overline{\mathcal{R}}_0(y) \varphi(y) dy \in L^1(\mathbb{R}).$$

Therefore, the existence of $\lambda^* > 0$ is strongly related to the spectral property of the operator \widehat{M} . Since \widehat{M} is positive, compact and irreducible, then from the Krein-Rutman theorem (see [18]), there exists an eigenfunction $\phi^* \in L^1(\mathbb{R})$, $\phi^* > 0$ normalized by $\|\phi^*\|_{L^1} = 1$ such that

$$\widehat{M}[\phi^*] = r(\widehat{M})\phi^*.$$

From (4.10), we find

$$r(\widehat{M}) = 1 + \mu_h^{-1} \int_{\mathbb{R}} \lambda^*(z) dz \quad \text{and} \quad \lambda^* = c^* \phi^*, \quad (4.11)$$

for some constant $c^* > 0$. It comes that $\mu_h(r(\widehat{M}) - 1) = \int_{\mathbb{R}} \lambda^*(z) dz > 0$, that is $r(\widehat{M}) > 1$. To compute $c^* > 0$, we replace $\lambda^* = c^* \phi^*$ in $r(\widehat{M})$ and we obtain

$$c^* = \mu_h(r(\widehat{M}) - 1).$$

It follows that system (4.1) has a unique positive endemic equilibrium when $r(\widehat{M}) > 1$, such that $\forall i \in \mathcal{I}$,

$$S_i^* = \frac{S_i^0}{r(\widehat{M})} \quad \text{and} \quad \mathbf{I}_i^*(\tau, x) = c^* \phi^*(x) S_i^* \mathbf{\Pi}_i(\tau, 0, x) \mathbf{p}_i(x),$$

where $c^* = \mu_h(r(\widehat{M}) - 1)$.

4.4 Technical materials

Before proceed to the proof Theorem 2.7, we introduce some technical materials including the existence of a global compact attractor for the solution semiflow of Model (4.1), the spectral properties of the linearized semiflow of Model (4.1) at any given equilibrium, and the uniform persistence of Model (4.1) when $r(\widehat{M}) > 1$.

4.4.1 Global compact attractor

To derive the global properties of the solution dynamics, it is necessary to show that the semiflow generated by system (4.1) has a global compact attractor. Denote by

$$\mathcal{Y} = \mathbb{R}^n \times L^1((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n}) \quad \text{and} \quad \mathcal{Y}_+ = \mathbb{R}_+^n \times L_+^1((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n}),$$

and endow the set \mathcal{Y} with the norm

$$\|(\mathbf{S}, \mathbf{I}(\cdot, \cdot))\| = \sum_{i \in \mathcal{I}} \left(|S_i| + \int_0^\infty \int_{\mathbb{R}} (|I_i^T(t, \tau, x)| + |I_i^U(t, \tau, x)|) dx d\tau \right).$$

For any initial condition $\varphi_0 \in \mathcal{Y}$, the solution semiflow of system (4.1) in \mathcal{Y}_+ is denoted by $\Psi^*(t, \varphi_0) = (\mathbf{S}(t), \mathbf{I}(t, \cdot, \cdot))^t$. From the Volterra formulation (4.4), we rewrite system (4.1) as follows :

$$\dot{S}_i(t) = \Lambda_i - S_i(t) \int_{\mathbb{R}} \lambda(t, x) dx - \mu_h S_i(t),$$

$$I_i^T(t, \tau, x) = \begin{cases} \Pi_{i,T}^T(\tau, \tau - t, x) I_{i0}^T(\tau - t, x) + \Pi_{i,U}^T(\tau, \tau - t, x) I_{i0}^U(\tau - t, x), & \text{if } t \leq \tau, \\ \Pi_i^T(\tau, 0, x) \lambda(t - \tau, x) S_i(t - \tau), & \text{if } t > \tau, \end{cases} \quad (4.12)$$

$$I_i^U(t, \tau, x) = \begin{cases} \Pi_{i,U}^U(\tau, \tau - t, x) I_{i0}^U(\tau - t, x) + \Pi_{i,U}^U(\tau, \tau - t, x) I_{i0}^U(\tau - t, x), & \text{if } t \leq \tau, \\ \Pi_i^U(\tau, 0, x) \lambda(t - \tau, x) S_i(t - \tau), & \text{if } t > \tau, \end{cases} \quad (4.13)$$

where

$$\Pi_i^T(\tau, 0, x) = \Pi_{i,T}^T(\tau, 0, x) p_i^T(x) + \Pi_{i,U}^T(\tau, 0, x) p_i^U(x) \quad \text{and} \quad \Pi_i^U(\tau, 0, x) = \Pi_{i,T}^U(\tau, 0, x) p_i^T(x) + \Pi_{i,U}^U(\tau, 0, x) p_i^U(x).$$

We need to prove the following claim.

Claim 4.3 *Let Assumption 2.1 and Remark 2.4 be satisfied. Then, $\forall x \in \mathbb{R}$, function $\bar{\lambda}(\cdot, x)$ is Lipschitz continuous on $L^1(\mathbb{R})$.*

Proof of Claim 4.3. Let $C_0 \geq \max \left\{ \frac{\bar{\Lambda}}{\mu_h}, \|\varphi_0\| \right\}$, $\|\beta_i\|_\infty = \max \left\{ \|\beta_i^T\|_\infty, \|\beta_i^U\|_\infty \right\}$ and $\|\beta\|_\infty = \sum_{i \in \mathcal{I}} \|\beta_i\|_\infty$. By Theorem 4.1, for all $x \in \mathbb{R}$ and $i \in \mathcal{J}$, there exists a bounded function $\bar{Q}_i(x) > 0$, $\bar{Q}_i \in L^1(\mathbb{R})$ such that $\int_0^\infty |I_i^T(t, \tau, x) + I_i^U(t, \tau, x)| d\tau < \bar{Q}_i(x)$. Let $t > 0$, $h > 0$ and $x \in \mathbb{R}$. It comes that

$$\begin{aligned} & \bar{\lambda}(t+h, x) - \bar{\lambda}(t, x) \\ &= \sum_{i \in \mathcal{I}} \int_0^h \langle \beta_i(\tau, x), \mathbf{I}_i(t+h, \tau, x) \rangle d\tau + \sum_{i \in \mathcal{I}} \int_h^\infty \langle \beta_i(\tau, x), \mathbf{I}_i(t+h, \tau, x) \rangle d\tau - \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau, x), \mathbf{I}_i(t, \tau, x) \rangle d\tau \\ &= \sum_{i \in \mathcal{I}} \int_0^h \langle \beta_i(\tau, x), \mathbf{\Pi}_i(\tau, 0, x) \mathbf{I}_i(t+h-\tau, 0, x) \rangle d\tau + \sum_{i \in \mathcal{I}} \int_h^\infty \langle \beta_i(\tau, x), \mathbf{I}_i(t+h, \tau, x) \rangle d\tau \\ & \quad - \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau, x), \mathbf{I}_i(t, \tau, x) \rangle d\tau. \end{aligned}$$

Since the semiflow is bounded, we can find $Q(x) = \int_{\mathbb{R}} K(x-y) \bar{Q}(y) dy > 0$, $\bar{Q}(x) = \sum_{i \in \mathcal{I}} \bar{Q}_i(x)$ such that

$$\begin{aligned} & \bar{\lambda}(t+h, x) - \bar{\lambda}(t, x) \\ & \leq C_0 \|\beta\|_\infty^2 Q(x) h + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau+h, x), \mathbf{I}_i(t+h, \tau+h, x) \rangle d\tau - \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau, x), \mathbf{I}_i(t, \tau, x) \rangle d\tau. \end{aligned}$$

Recalling (4.4) and combining the integrals, we obtain

$$\begin{aligned} \bar{\lambda}(t+h, x) - \bar{\lambda}(t, x) & \leq C_0 \|\beta\|_\infty^2 Q(x) h + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau+h, x), (\mathbf{\Pi}_i(\tau+h, \tau, x) - \mathbb{I}) \mathbf{I}_i(t, \tau, x) \rangle d\tau \\ & \quad + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau+h, x) - \beta_i(\tau, x), \mathbf{I}_i(t, \tau, x) \rangle d\tau \\ & \leq C_0 \|\beta\|_\infty^2 Q(x) h + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau+h, x), (\gamma_1 e^{-\mu_h h} - 1) \mathbf{I}_i(t, \tau, x) \rangle d\tau \\ & \quad + \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(\tau+h, x) - \beta_i(\tau, x), \mathbf{I}_i(t, \tau, x) \rangle d\tau. \end{aligned}$$

We have $|\gamma_1 e^{-\mu_h h} - 1| \leq \gamma_1 \mu_h h$. Using the Lipschitzianity of β_i^{ϑ} , we find a positive constant C_β such that

$$|\bar{\lambda}(t+h, x) - \bar{\lambda}(t, x)| \leq C_0 \|\beta\|_\infty^2 Q(x)h + \|\beta\|_\infty \mu_h \gamma_1 Q(x)h + C_\beta Q(x)h \leq C_\lambda(x)h,$$

where $C_\lambda(x) = C_0 \|\beta\|_\infty^2 Q(x) + \|\beta\|_\infty \mu_h \gamma_1 Q(x) + C_\beta Q(x)$. \blacksquare

Next, we will show that system (4.1) has a global attractor. By using the similar method as in [8, 10, 37], we can state the following result.

Lemma 4.4 *There exists \mathcal{A}_0 , a compact subset of \mathcal{Y}_+ , which is a global attractor for the solution semiflow of system (4.1). Moreover, \mathcal{A}_0 is invariant under the solution semiflow, that is*

$$\Psi^*(t, \varphi_0) \subseteq \mathcal{A}_0, \quad \text{for every } \varphi_0 \in \mathcal{A}_0, \quad \forall t \geq 0.$$

Proof. We show that Ψ^* satisfies the assumptions of Lemma 3.2.3 and Theorem 3.4.6 in [24]. To this end, we split the solution semiflow into two parts. For any initial condition $\varphi_0 \in \mathcal{Y}_+$, we let $\Psi^*(t, \varphi_0) = \widehat{\Psi}^*(t, \varphi_0) + \widetilde{\Psi}^*(t, \varphi_0)$, where

$$\widehat{\Psi}^*(t, \varphi_0) = \begin{cases} (\mathbf{0}_{\mathbb{R}^n}, \mathbf{0}_{L^1}), & t > \tau, \\ (\mathbf{0}_{\mathbb{R}^n}, \mathbf{I}(t, \tau, x)), & t \leq \tau, \end{cases} \quad \text{and} \quad \widetilde{\Psi}^*(t, \varphi_0) = \begin{cases} (\mathbf{S}(t), \mathbf{I}(t, \tau, x)), & t > \tau, \\ (\mathbf{S}(t), \mathbf{0}_{L^1}), & t \leq \tau. \end{cases}$$

In such a way, we need to prove the following claim :

Claim 4.5 (1) $\widehat{\Psi}^*(t, \varphi_0) \rightarrow 0$ as $t \rightarrow \infty$ for every φ_0 in \mathcal{Y} .

(2) For a fixed t and any bounded set B in \mathcal{Y} , the set $\{\widetilde{\Psi}^*(t, \varphi_0) : \varphi_0 \in B\}$ is precompact.

Proof of Claim 4.5. Now, we show that the first claim holds.

From (4.12) and Lemma 4.2, we have

$$\begin{aligned} \|\widehat{\Psi}^*(t, \varphi_0)\| &= \sum_{i \in \mathcal{I}} \int_{\mathbb{R}} \int_0^\infty (|I_i^T(t, \tau, x)| + |I_i^U(t, \tau, x)|) d\tau dx \\ &= \sum_{i \in \mathcal{I}} \int_{\mathbb{R}} \int_0^\infty [\Pi_{i,T}^T(\tau, \tau - t, x) + \Pi_{i,T}^U(\tau, \tau - t, x)] I_{i0}^T(\tau - t, x) d\tau dx \\ &\quad + \sum_{i \in \mathcal{I}} \int_{\mathbb{R}} \int_0^\infty [\Pi_{i,U}^T(\tau, \tau - t, x) + \Pi_{i,U}^U(\tau, \tau - t, x)] I_{i0}^U(\tau - t, x) d\tau dx \\ &\leq 2\gamma_1 e^{-\mu_h t} \|\varphi_0\|. \end{aligned}$$

Define $k(r, t) = 2r\gamma_1 e^{-\mu_h t}$. Then, $k(r, t) \rightarrow 0$ as $t \rightarrow \infty$ and $\|\widehat{\Psi}^*(t, \varphi_0)\| \leq k(r, t)$ for $\|\varphi_0\| \leq r$. This complete the first claim.

To show that the second claim holds, let $B \subset \mathcal{Y}$ be a bounded subset such that $\Psi^*(t, \cdot)B \subset B$. Choose $C_0 > 0$ such that $\|\varphi_0\| \leq C_0$ for all $\varphi_0 \in B$. From Theorem 4.1 Item 2, $\cup_{\varphi_0 \in B} \{\mathbf{S}(t)\}$ is bounded in \mathbb{R}^n and then is precompact in \mathbb{R}^n . Hence, to show the compactness, it suffices to show that the set $\widetilde{\Psi}^*(t, \varphi_0)B$ is precompact for

$$\widetilde{\mathbf{I}}(t, \tau, x) = \begin{cases} \mathbf{I}(t, \tau, x), & t > \tau, \\ \mathbf{0}_{L^1}, & t \leq \tau. \end{cases} \quad (4.14)$$

By Frechet-Kolmogorov theorem (see Theorem B.2 in [41]), it is sufficient to verify the following conditions :

- (i) $\sup_{\varphi_0 \in B} \sum_{i \in \mathcal{I}} \int_{\mathbb{R}} \int_0^\infty (\widetilde{I}_i^T(t, \tau, x) + \widetilde{I}_i^U(t, \tau, x)) d\tau dx < \infty,$
- (ii) $\lim_{(h,k) \rightarrow \infty} \sum_{i \in \mathcal{I}} \int_k^\infty \int_h^\infty (|\widetilde{I}_i^T(t, \tau, x)| + |\widetilde{I}_i^U(t, \tau, x)|) d\tau dx = 0$ uniformly with respect to $\varphi_0 \in B$.

$$(iii) \quad \lim_{(h,k) \rightarrow (0,0)} \sum_{i \in \mathcal{I}} \int_{\mathbb{R}} \int_0^\infty \left(|\tilde{I}_i^T(t, \tau, x) - \tilde{I}_i^T(t, \tau + h, x + k)| + |\tilde{I}_i^U(t, \tau, x) - \tilde{I}_i^U(t, \tau + h, x + k)| \right) d\tau dx = 0$$

uniformly with respect to $\varphi_0 \in B$.

$$(iv) \quad \lim_{(h,k) \rightarrow (0,0)} \sum_{i \in \mathcal{I}} \int_0^k \int_0^h \left(|\tilde{I}_i^T(t, \tau, x)| + |\tilde{I}_i^U(t, \tau, x)| \right) d\tau dx = 0 \text{ uniformly with respect to } \varphi_0 \in B.$$

By (4.14) and Lemme 4.2, we have for all $i \in \mathcal{I}$

$$\tilde{\mathbf{I}}_i(t, \tau, x) = \begin{cases} \lambda(t - \tau, x) S_i(t - \tau) \mathbf{\Pi}_i(\tau, 0, x) \mathbf{p}_i(x), & t > \tau, \\ \mathbf{0}_{L^1}, & t \leq \tau. \end{cases} \leq \gamma_1 e^{-\mu_h \tau} C_{i0} \|\beta\|_\infty Q(x) \mathbf{p}_i(x),$$

where $Q(x) = \int_{\mathbb{R}} K(x - y) \bar{Q}(y) dy$. It follows that above conditions (i), (ii) and (iv) are satisfied.

Now, we show that condition (iii) holds. We have for $i \in \mathcal{I}$,

$$\begin{aligned} & \int_{\mathbb{R}} \int_0^\infty |\tilde{I}_i^T(t, \tau + h, x + k) - \tilde{I}_i^T(t, \tau, x)| d\tau dx \\ &= \int_{\mathbb{R}} \int_0^\infty |\tilde{I}_i^T(t, \tau + h, x + k) - \tilde{I}_i^T(t, \tau, x + k) + \tilde{I}_i^T(t, \tau, x + k) - \tilde{I}_i^T(t, \tau, x)| d\tau dx \\ &\leq \int_{\mathbb{R}} \int_0^\infty |\tilde{I}_i^T(t, \tau + h, x + k) - \tilde{I}_i^T(t, \tau, x + k)| d\tau dx + \int_{\mathbb{R}} \int_0^\infty |\tilde{I}_i^T(t, \tau, x + k) - \tilde{I}_i^T(t, \tau, x)| d\tau dx. \end{aligned}$$

On the one hand, we have for $h \leq t$,

$$\begin{aligned} & \int_{\mathbb{R}} \int_0^\infty |\tilde{I}_i^T(t, \tau, x + k) - \tilde{I}_i^T(t, \tau + h, x + k)| d\tau dx \\ &= \int_{\mathbb{R}} \int_0^{t-h} \left| \Pi_i^T(\tau, 0, x + k) \lambda(t - \tau, x + k) S_i(t - \tau) - \Pi_i^T(\tau + h, 0, x + k) \lambda(t - \tau - h, x + k) S_i(t - \tau - h) \right| d\tau dx \\ & \quad + \int_{\mathbb{R}} \int_{t-h}^t \left| \Pi_i^T(\tau, 0, x + k) \lambda(t - \tau, x + k) S_i(t - \tau) \right| d\tau dx \\ &\leq \int_{\mathbb{R}} \int_0^{t-h} \gamma_1 e^{-\mu_h \tau} \lambda(t - \tau, x + k) S_i(t - \tau) \left| 1 - \frac{\Pi_i^T(\tau + h, 0, x + k)}{\Pi_i^T(\tau, 0, x + k)} \right| d\tau dx \\ & \quad + \int_{\mathbb{R}} \int_0^{t-h} \gamma_1 e^{-\mu_h \tau} \frac{\Pi_i^T(\tau + h, 0, x + k)}{\Pi_i^T(\tau, 0, x + k)} \left| \lambda(t - \tau, x + k) S_i(t - \tau) - \lambda(t - \tau - h, x + k) S_i(t - \tau - h) \right| d\tau dx \\ & \quad + \int_{\mathbb{R}} \int_{t-h}^t \left| \Pi_i^T(\tau, 0, x + k) \lambda(t - \tau, x + k) S_i(t - \tau) \right| d\tau dx \\ &:= C_1(t, h) + C_2(t, h) + C_3(t, h). \end{aligned}$$

Note that

$$C_1(t, h) \leq \int_0^\infty \gamma_1 C_{i0} \|\beta\|_\infty e^{-\mu_h \tau} \int_{\mathbb{R}} Q(x + k) \left| 1 - \frac{\Pi_i^T(\tau + h, 0, x + k)}{\Pi_i^T(\tau, 0, x + k)} \right| dx d\tau \rightarrow 0 \quad \text{as } h \rightarrow 0 \quad (4.15)$$

and

$$C_3(t, h) = \int_{\mathbb{R}} \int_{t-h}^t \left| \Pi_i^T(\tau, 0, x + k) \lambda(t - \tau, x + k) S_i(t - \tau) \right| d\tau dx \leq \gamma_1 C_{i0} \|\lambda\|_{L^1} h \rightarrow 0 \quad \text{as } h \rightarrow 0. \quad (4.16)$$

From Lemma 4.2, there exists a constant $\delta > 0$ such that $\frac{\Pi_i^T(\tau+h,0,x+k)}{\Pi_i^T(\tau,0,x+k)} < \delta$. Hence,

$$\begin{aligned}
C_2(t, h) &= \int_{\mathbb{R}} \int_0^{t-h} \gamma_1 e^{-\mu_h \tau} \frac{\Pi_i^T(\tau+h, 0, x+k)}{\Pi_i^T(\tau, 0, x+k)} \left| \lambda(t-\tau, x+k) S_i(t-\tau) - \lambda(t-\tau-h, x+k) S_i(t-\tau-h) \right| d\tau dx \\
&\leq \gamma_1 \delta \int_{\mathbb{R}} \int_0^{t-h} e^{-\mu_h \tau} S_i(t-\tau) \left| \lambda(t-\tau, x+k) - \lambda(t-\tau-h, x+k) \right| d\tau dx \\
&\quad + \gamma_1 \delta \int_{\mathbb{R}} \int_0^{t-h} e^{-\mu_h \tau} \lambda(t-\tau-h, x+k) \left| S_i(t-\tau) - S_i(t-\tau-h) \right| d\tau dx \\
&\leq \left(\gamma_1 \delta C_{i0} \|C_\lambda\|_{L^1} h + \gamma_1 \delta \|\lambda\|_{L^1} C_{S_i} h \right) \int_0^{t-h} e^{-\mu_h \tau} d\tau \leq \frac{\gamma_1 \delta}{\mu_h} \left(C_{i0} \|C_\lambda\|_{L^1} + \|\lambda\|_{L^1} C_{S_i} \right) h,
\end{aligned}$$

where $C_{S_i} = \Lambda_i + C_{i0}(\|\lambda\|_{L^1} + \mu_h)$. It follows that

$$C_2(t, h) \leq \frac{\gamma_1 \delta}{\mu_h} \left(C_{i0} \|C_\lambda\|_{L^1} + \|\lambda\|_{L^1} C_{S_i} \right) h \rightarrow 0 \quad \text{as } h \rightarrow 0. \quad (4.17)$$

On the other hand, we have

$$\begin{aligned}
&\int_{\mathbb{R}} \int_0^\infty |\tilde{I}_i^T(t, \tau, x+k) - \tilde{I}_i^T(t, \tau, x)| d\tau dx \\
&= \int_{\mathbb{R}} \int_0^\infty S_i(t-\tau) \left| \Pi_i^T(\tau, 0, x+k) \lambda(t-\tau, x+k) - \Pi_i^T(\tau, 0, x) \lambda(t-\tau, x) \right| d\tau dx \\
&\leq \int_{\mathbb{R}} \int_0^t \lambda(t-\tau, x+k) S_i(t-\tau) \left| \Pi_i^T(\tau, 0, x+k) - \Pi_i^T(\tau, 0, x) \right| d\tau dx \\
&\quad + \int_{\mathbb{R}} \int_0^t S_i(t-\tau) \Pi_i^T(\tau, 0, x) \left| \lambda(t-\tau, x+k) - \lambda(t-\tau, x) \right| d\tau dx \\
&\leq C_{i0} \gamma_1 \|\beta\|_\infty \int_{\mathbb{R}} \int_0^t e^{-\mu_h \tau} Q(x+k) \left| \frac{\Pi_i^T(\tau, 0, x+k)}{\Pi_i^T(\tau, 0, x)} - 1 \right| d\tau dx \\
&\quad + C_{i0} \gamma_1 \int_{\mathbb{R}} \int_0^t e^{-\mu_h \tau} \left| \lambda(t-\tau, x+k) - \lambda(t-\tau, x) \right| d\tau dx \\
&\leq C_{i0} \gamma_1 \|\beta\|_\infty \int_{\mathbb{R}} \int_0^t e^{-\mu_h \tau} Q(x+k) \left| \frac{\Pi_i^T(\tau, 0, x+k)}{\Pi_i^T(\tau, 0, x)} - 1 \right| d\tau dx \\
&\quad + C_{i0} \gamma_1 \|\bar{\lambda}\|_{L^1} \|\mathbf{T}_k[K] - K\|_{L^1(\mathbb{R})} \int_0^t e^{-\mu_h \tau} d\tau,
\end{aligned}$$

where \mathbf{T}_k is the translation operator in L^1 , i.e. $\mathbf{T}_k[v] = v(\cdot + k)$ for each $v \in L^1(\mathbb{R})$. It follows that

$$\begin{aligned}
&\int_{\mathbb{R}} \int_0^\infty |\tilde{I}_i^T(t, \tau, x+k) - \tilde{I}_i^T(t, \tau, x)| d\tau dx \\
&\leq C_{i0} \gamma_1 \|\beta\|_\infty \int_{\mathbb{R}} \int_0^\infty e^{-\mu_h \tau} Q(x+k) \left| \frac{\Pi_i^T(\tau, 0, x+k)}{\Pi_i^T(\tau, 0, x)} - 1 \right| d\tau dx + \frac{C_{i0} \gamma_1}{\mu_h} \|\bar{\lambda}\|_{L^1} \|\mathbf{T}_k[K] - K\|_{L^1(\mathbb{R})} \rightarrow 0 \quad \text{as } k \rightarrow 0.
\end{aligned} \quad (4.18)$$

By (4.15), (4.16), (4.17) and (4.18) one concludes that the criterion (iii) holds, and then the second claim holds. \blacksquare

This completes the proof of the lemma. \blacksquare

4.4.2 Spectral properties of the linearized semiflow

The next result is concerned with spectral properties of the linearized semiflow Ψ of Model (4.1) at a given equilibrium point $\tilde{\varphi} \in \mathcal{X}_{0+}$. The associated linearized system (4.1) at the point $\tilde{\varphi}$ reads as

$$\frac{d\varphi(t)}{dt} = (A + G[\tilde{\varphi}])\varphi(t),$$

where A is the linear operator defined in (4.2) while $G[\tilde{\varphi}] \in \mathcal{L}(\mathcal{X}_0, \mathcal{X})$ is the bounded linear operator defined by :

$$G[\tilde{\varphi}]\varphi = \begin{pmatrix} -\mathbf{S} \int_{\mathbb{R}} \tilde{\lambda}(x) dx - \tilde{\mathbf{S}} \int_{\mathbb{R}} \lambda(x) dx \\ \tilde{\lambda}(x) \text{diag}(\mathbf{S}) \mathbf{p}(x) + \lambda(x) \text{diag}(\tilde{\mathbf{S}}) \mathbf{p}(x) \\ \mathbf{0}_{L^1((0,\infty) \times \mathbb{R}, \mathbb{R}^{2n})} \end{pmatrix},$$

where $\tilde{\lambda}(x) = \int_{\mathbb{R}} K(x-y) \sum_i \int_0^\infty \langle \beta_i(b_i(\tau, y)), \tilde{\mathbf{I}}_i(\tau, y) \rangle d\tau dy$ and $\lambda(x) = \int_{\mathbb{R}} K(x-y) \sum_i \int_0^\infty \langle \beta_i(b_i(\tau, y)), \mathbf{I}_i(\tau, y) \rangle d\tau dy$. We then have the following lemma.

Lemma 4.6 *Let us set $\Omega = \{\nu \in \mathbb{C} : \text{Re}(\nu) > -\mu_h\}$. Denote by Σ the spectrum of $A + G[\tilde{\varphi}]$ in Ω . Then, Σ is the set of $\nu \in \Omega$ such that there exists a positive functional $\lambda \in L^1_+(\mathbb{R})$ for which*

$$\lambda(x) - \mathcal{L}_\nu[\tilde{\varphi}]\lambda(x) + \frac{\mathcal{L}_\nu[\tilde{\varphi}]\tilde{\lambda}(x) \int_{\mathbb{R}} \lambda(z) dz}{\nu + \mu_h + \int_{\mathbb{R}} \tilde{\lambda}(z) dz} = 0,$$

where for all $\psi \in L^1(\mathbb{R})$,

$$\mathcal{L}_\nu[\tilde{\varphi}]\psi(x) = \int_{\mathbb{R}} K(x-y) \mathcal{R}_\nu[\tilde{\varphi}](y) \psi(y) dy,$$

with $\mathcal{R}_\nu[\tilde{\varphi}](x) = \sum_{i \in \mathcal{I}} \tilde{S}_i \int_0^\infty \langle \beta_i(b_i(\tau, x)), \mathbf{\Pi}_i(\tau, 0, x) \mathbf{p}_i(x) \rangle e^{-\nu\tau} d\tau$.

Proof.

Let us denote by $A_0 : D(A_0) \subset \mathcal{X}_0 \rightarrow \mathcal{X}_0$ the part of A in $\mathcal{X}_0 = D(A)$, which is defined by

$$A_0\varphi = A\varphi, \quad \forall \varphi \in D(A_0) = \{\varphi \in D(A) : A\varphi \in D(A)\}.$$

Then, it is the infinitesimal generator of a C_0 -semigroup on \mathcal{X}_0 denoted by $\{T_{A_0}(t)\}_{t \geq 0}$. Let $\varphi = (\mathbf{S}, \mathbf{0}_{L^1}, \mathbf{I}(\cdot, \cdot))^t$. We find that

$$T_{A_0}(t)\varphi(\tau, x) = \begin{cases} \left(e^{-\mu_h t} \mathbf{S}, \mathbf{0}_{L^1(\mathbb{R}, \mathbb{R}^{2n})}, \mathbf{\Pi}(\tau, \tau - t, x) \mathbf{I}(\tau - t, x) \right)^t, & \forall t \leq \tau, \\ \left(e^{-\mu_h t} \mathbf{S}, \mathbf{0}_{L^1(\mathbb{R}, \mathbb{R}^{2n})}, \mathbf{0}_{L^1((0,\infty) \times \mathbb{R}, \mathbb{R}^{2n})} \right)^t, & \forall t > \tau. \end{cases}$$

Then, for $t \geq \tau_0$, we have $\|T_{A_0}(t - \tau_0)\varphi\|_{\mathcal{X}} \leq e^{-\mu_h(t - \tau_0)} \|\varphi\|_{\mathcal{X}}, \forall t \geq \tau_0$. We deduce that the growth rate $\omega_0(A_0) = \lim_{t \rightarrow +\infty} \frac{\ln(\|T_{A_0}(t)\|_{\mathcal{L}(\mathcal{X})})}{t}$ of this semigroup satisfies $\omega_0(A_0) \leq -\mu_h$. Since operator $G_i[\tilde{\varphi}]$ is compact, the results in [4] or [19] apply and provided that the essential growth rate of $\left\{ T_{(A+G[\tilde{\varphi}])_0}(t) \right\}_{t \geq 0}$ - the C_0 -semigroup generated by the part of $(A + G[\tilde{\varphi}])$ in \mathcal{X}_0 satisfies

$$\omega_{0,ess}((A + G[\tilde{\varphi}])_0) \leq \omega_{0,ess}(A_0) < \omega_0(A_0) \leq -\mu_h.$$

By results in [21, 45], the latter inequality ensures that $\Omega \cap \sigma(A + G[\tilde{\varphi}]) \neq \emptyset$, and it is only composed of point spectrum of $(A + G[\tilde{\varphi}])$.

It remains to derive the characteristic equation. Let $\nu \in \rho(A + G[\tilde{\varphi}])$, where $\rho(\cdot)$ stands for the resolvent. For $\hat{\varphi} = (\hat{\mathbf{S}}, \hat{\mathbf{q}}, \hat{\mathbf{I}}(\cdot, \cdot))^t \in \mathcal{X}$ and $\varphi = (\mathbf{S}, \mathbf{0}_{L^1}, \mathbf{I}(\cdot, \cdot))^t \in D(A)$, we have $(\nu I - A - G[\tilde{\varphi}])\varphi = \hat{\varphi}$, that is $(\nu I - A)\varphi - G[\tilde{\varphi}]\varphi = \hat{\varphi}$, and from where

$$\varphi = (\nu I - A)^{-1} \hat{\varphi} + (\nu I - A)^{-1} G[\tilde{\varphi}]\varphi. \quad (4.19)$$

Since

$$(\nu I - A)^{-1} \hat{\varphi} = \left(\left(\frac{\hat{S}_i}{\nu + \mu_h} \right)_{i \in \mathcal{I}}, \mathbf{0}_{L^1(\mathbb{R}, \mathbb{R}^{2n})}, \left(e^{-\nu \cdot} \mathbf{\Pi}_i(\cdot, 0, x) \hat{\mathbf{q}}_i + \int_0^\cdot \mathbf{\Pi}_i(\cdot, s, x) \hat{\mathbf{I}}_i(s, x) e^{-\nu(\cdot-s)} ds \right)_{i \in \mathcal{I}} \right)^t,$$

we find that

$$(\nu I - A)^{-1}G[\tilde{\varphi}]\boldsymbol{\varphi} = \begin{pmatrix} \left(\frac{-S_i \int_{\mathbb{R}} \tilde{\lambda}(x) dx - \tilde{S}_i \int_{\mathbb{R}} \lambda(x) dx}{\nu + \mu_h} \right)_{i \in \mathcal{I}} \\ \mathbf{0}_{L^1(\mathbb{R}, \mathbb{R}^{2n})} \\ \left(e^{-\nu \cdot} \mathbf{\Pi}_i(\cdot, 0, x) \left(S_i \tilde{\lambda}(x) \mathbf{p}_i(x) + \tilde{S}_i \lambda(x) \mathbf{p}_i(x) \right) \right)_{i \in \mathcal{I}} \end{pmatrix}.$$

Thus, for all $i \in \mathcal{I}$, equality (4.19) rewrites as

$$\begin{aligned} & \left(1 + \frac{\int_{\mathbb{R}} \tilde{\lambda}(x) dx}{\nu + \mu_h} \right) S_i + \frac{\tilde{S}_i \int_{\mathbb{R}} \lambda(x) dx}{\nu + \mu_h} = \frac{\hat{S}_i}{\nu + \mu_h}, \\ & \begin{cases} S_i = \frac{\hat{S}_i}{\nu + \mu_h + \int_{\mathbb{R}} \tilde{\lambda}(x) dx} - \frac{\tilde{S}_i \int_{\mathbb{R}} \lambda(x) dx}{\nu + \mu_h + \int_{\mathbb{R}} \tilde{\lambda}(x) dx} \\ \mathbf{I}_i(\tau, x) = e^{-\nu \tau} \mathbf{\Pi}_i(\tau, 0, x) \left(S_i \tilde{\lambda}(x) \mathbf{p}_i(x) + \tilde{S}_i \lambda(x) \mathbf{p}_i(x) \right) + e^{-\nu \tau} \mathbf{\Pi}_i(\tau, 0, x) \hat{\mathbf{q}}_i \\ \quad + \int_0^\tau \mathbf{\Pi}_i(\tau, s, x) \hat{\mathbf{I}}_i(s, x) e^{-\nu(\tau-s)} ds. \end{cases} \end{aligned} \quad (4.20)$$

Substituting (4.20) into expression for $\lambda(x)$, it comes

$$\begin{aligned} & \lambda(x) - \int_{\mathbb{R}} K(x-y) \mathcal{R}_\nu[\tilde{\varphi}](y) \lambda(y) dy + \frac{\int_{\mathbb{R}} K(x-y) \mathcal{R}_\nu[\tilde{\varphi}](y) \tilde{\lambda}(y) dy}{\nu + \mu_h + \int_{\mathbb{R}} \tilde{\lambda}(z) dz} \int_{\mathbb{R}} \lambda(x) dx \\ & = \frac{\int_{\mathbb{R}} K(x-y) \mathcal{R}_\nu[\tilde{\varphi}](y) \tilde{\lambda}(y) dy}{\nu + \mu_h + \int_{\mathbb{R}} \tilde{\lambda}(z) dz} + \int_{\mathbb{R}} K(x-y) \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(b_i(\tau, y)), \hat{\mathbf{y}}_i(\tau, y) \rangle d\tau dy, \end{aligned} \quad (4.21)$$

where $\mathcal{R}_\nu[\tilde{\varphi}](x) = \sum_{i \in \mathcal{I}} \tilde{S}_i \int_0^\infty \langle \beta_i(b_i(\tau, x)), \mathbf{\Pi}_i(\tau, 0, x) \mathbf{p}_i(x) \rangle e^{-\nu \tau} d\tau$ and $\hat{\mathbf{y}}_i(\tau, x) = e^{-\nu \tau} \mathbf{\Pi}_i(\tau, 0, x) \hat{\mathbf{q}}_i + \int_0^\tau \mathbf{\Pi}_i(\tau, s, x) \hat{\mathbf{I}}_i(s, x) e^{-\nu(\tau-s)} ds$.

Setting,

$$\mathcal{L}_\nu[\tilde{\varphi}]\psi(x) = \int_{\mathbb{R}} K(x-y) \mathcal{R}_\nu[\tilde{\varphi}](y) \psi(y) dy, \quad (4.22)$$

the above equality rewrites

$$\lambda(x) - \mathcal{L}_\nu[\tilde{\varphi}]\lambda(x) + \frac{\mathcal{L}_\nu[\tilde{\varphi}]\tilde{\lambda}(x)}{\nu + \mu_h + \int_{\mathbb{R}} \tilde{\lambda}(z) dz} \int_{\mathbb{R}} \lambda(x) dx = f[\tilde{\varphi}, \hat{\varphi}](x), \quad (4.23)$$

with $f[\tilde{\varphi}, \hat{\varphi}](x) = \frac{\mathcal{L}_\nu[\tilde{\varphi}]\tilde{\lambda}(x)}{\nu + \mu_h + \int_{\mathbb{R}} \tilde{\lambda}(z) dz} + \int_{\mathbb{R}} K(x-y) \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(b_i(\tau, y)), \hat{\mathbf{y}}_i(\tau, y) \rangle d\tau dy$. ■

5 Proof of Theorem 2.7

To study the local stability of the disease-free equilibrium of System (4.1), we have to know the structure of spectral properties of the linearized semiflow of System (4.1) at the disease-free equilibrium \mathbf{E}^0 . Recalling Lemma 4.6 at the disease-free equilibrium \mathbf{E}^0 , the set of characteristic value is given by

$$\Sigma := \sigma(A + G[\mathbf{E}^0]) = \left\{ \nu \in \mathbb{C} : 1 \in \sigma(\mathcal{L}_\nu[\mathbf{E}^0]) \right\},$$

where $\mathcal{L}_\nu[\mathbf{E}^0]$ is defined in (4.22).

In the following, we will use elements of positive operator theory on ordered Banach spaces (see [27]). Next, we give some properties of $\mathcal{L}_\nu[\mathbf{E}^0]$.

Lemma 5.1 *Let Assumption 2.1 and Remark 2.4 be satisfied. Then the operator $\mathcal{L}_\nu[\mathbf{E}^0]$ is compact and non-supporting for all $\nu \in \mathbb{R}$.*

Proof. Under Assumption 2.1 and Remark 2.4, it is easy to see from the well-known compactness criterium in L^1 that the operator $\mathcal{L}_\nu[\mathbf{E}^0]$ is compact for all $\nu \in \mathbb{C}$. Next, for $\nu \in \mathbb{R}$, we can be checked that

$$\mathcal{L}_\nu[\mathbf{E}^0]\psi \geq \langle G_\nu, \psi \rangle \cdot e, \quad \psi \in L_+^1(\mathbb{R}), \quad e \equiv 1 \in L_+^1(\mathbb{R}), \quad (5.1)$$

where $G_\nu \in (L^1(\mathbb{R}))'$ is a positive linear functional defined by

$$\langle G_\nu, \psi \rangle := \gamma_0 \int_{\mathbb{R}} K(x-y) \left(\sum_{i \in \mathcal{J}} S_i^0 \int_0^\infty \langle \beta_i(b_i(\tau, y)), \mathbf{p}_i(y) \rangle e^{-\nu\tau} d\tau \right) \psi(y) dy,$$

with γ_0 given in Lemma 4.2. Moreover, for any $n \in \mathbb{N}$, we have

$$\mathcal{L}_\nu^{n+1}[\mathbf{E}^0]\psi \geq \langle G_\nu, \psi \rangle \langle G_\nu, e \rangle^n \cdot e.$$

Hence, we obtain $\langle G, \mathcal{L}_\nu^{n+1}[\mathbf{E}^0]\psi \rangle > 0$, $n \geq 1$ for every pair $\psi \in L_+^1 \setminus \{0\}$, $G \in (L_+^1)' \setminus \{0\}$, that is $\mathcal{L}_\nu[\mathbf{E}^0]$ is a non-supporting operator. \blacksquare

Moreover, we have the following lemma.

Lemma 5.2 *Assumption 2.1 and Remark 2.4, the following holds :*

(i) $\Sigma = \sigma_p(A + G[\mathbf{E}^0]) = \left\{ \nu \in \mathbb{C} : 1 \in \sigma_p(\mathcal{L}_\nu[\mathbf{E}^0]) \right\}$, where $\sigma_p(T)$ denotes the set of point spectrum of the operator T .

(ii) The spectral radius $r(\mathcal{L}_\nu[\mathbf{E}^0])$, $\nu \in \mathbb{R}$ is strictly decreasing and,

$$\lim_{\nu \rightarrow -\infty} r(\mathcal{L}_\nu[\mathbf{E}^0]) = +\infty \quad \text{and} \quad \lim_{\nu \rightarrow +\infty} r(\mathcal{L}_\nu[\mathbf{E}^0]) = 0.$$

(iii) There exists a unique $\nu_0 \in \mathbb{R} \cap \Sigma$ such that

$$r(\mathcal{L}_{\nu_0}[\mathbf{E}^0]) = 1 \quad \text{and} \quad \begin{cases} \nu_0 > 0 & \text{if } r(\mathcal{L}_0[\mathbf{E}^0]) > 1, \\ \nu_0 = 0 & \text{if } r(\mathcal{L}_0[\mathbf{E}^0]) = 1, \\ \nu_0 < 0 & \text{if } r(\mathcal{L}_0[\mathbf{E}^0]) < 1. \end{cases}$$

(iv) $\nu_0 > \sup \left\{ \Re \nu : \nu \in \Sigma \setminus \{\nu_0\} \right\}$.

Proof.

(i) Since $\mathcal{L}_\nu[\mathbf{E}^0]$ is compact, $\sigma(\mathcal{L}_\nu[\mathbf{E}^0]) \setminus \{0\} = \sigma_p(\mathcal{L}_\nu[\mathbf{E}^0]) \setminus \{0\}$, hence (i) follows.

(ii) Let $f : \mathbb{R} \rightarrow \mathbb{C}$, $\nu \mapsto r(\mathcal{L}_\nu[\mathbf{E}^0])$ and $\nu_1, \nu_2 \in \mathbb{R}$ such that $\nu_1 < \nu_2$. Since $\mathcal{R}_\nu[\mathbf{E}^0]$ is strictly decreasing with respect to $\nu \in \mathbb{R}$, it follows that $\mathcal{R}_{\nu_1}[\mathbf{E}^0] > \mathcal{R}_{\nu_2}[\mathbf{E}^0]$, that is, $\mathcal{L}_{\nu_1}[\mathbf{E}^0] > \mathcal{L}_{\nu_2}[\mathbf{E}^0]$. Since $\mathcal{L}_{\nu_1}[\mathbf{E}^0]$ and $\mathcal{L}_{\nu_2}[\mathbf{E}^0]$ are compact and non-supporting operators, we deduce that $r(\mathcal{L}_{\nu_1}[\mathbf{E}^0]) > r(\mathcal{L}_{\nu_2}[\mathbf{E}^0])$ i.e. $f(\nu_1) > f(\nu_2)$. Hence, the function f is strictly decreasing. Moreover, let ϕ_ν be the positive eigenfunctional of $\mathcal{L}_\nu[\mathbf{E}^0]$ that corresponds to the eigenvalue $r(\mathcal{L}_\nu[\mathbf{E}^0])$. From (5.1), we have $r(\mathcal{L}_\nu[\mathbf{E}^0]) \langle \phi_\nu, \psi \rangle \geq \langle G_\nu, \psi \rangle \langle \phi_\nu, e \rangle$. Taking $\psi = e$, it follows that $r(\mathcal{L}_\nu[\mathbf{E}^0]) \geq \langle G_\nu, e \rangle \rightarrow +\infty$ as $\nu \rightarrow -\infty$. Hence, $\lim_{\nu \rightarrow -\infty} r(\mathcal{L}_\nu[\mathbf{E}^0]) = +\infty$. Since $\|\mathcal{L}_\nu[\mathbf{E}^0]\|_{L^1} \rightarrow 0$ when $\nu \rightarrow +\infty$, then we obtain $\lim_{\nu \rightarrow +\infty} r(\mathcal{L}_\nu[\mathbf{E}^0]) = 0$. This ends the proof of item (ii).

- (iii) The limits of the function f at $-\infty$ and $+\infty$ give that there exists a unique $\nu_0 \in \mathbb{R} \cap \Sigma$ such that $r(\mathcal{L}_{\nu_0}[\mathbf{E}^0]) = 1$. It follows that if $r(\mathcal{L}_0[\mathbf{E}^0]) > 1$ then $f(0) > f(\nu_0)$ which implies that $\nu_0 > 0$ because the function f is strictly decreasing. If $r(\mathcal{L}_0[\mathbf{E}^0]) < 1$ then $f(0) < f(\nu_0)$ which implies that $\nu_0 < 0$. Finally, $r(\mathcal{L}_0[\mathbf{E}^0]) = r(\mathcal{L}_{\nu_0}[\mathbf{E}^0]) = 1$ implies $\nu_0 = 0$. Hence, item (iii) follows.
- (iv) We can use the idea in Proposition 3.3 in [27] to show result (iv). Let $\nu \in \Sigma$. There exists $\phi^* \in L^1(\mathbb{R})$ such that $\mathcal{L}_\nu[\mathbf{E}^0]\phi^* = \phi^*$. We have, $|\phi^*| = |\mathcal{L}_\nu[\mathbf{E}^0]\phi^*| \leq \mathcal{L}_{\Re(\nu)}[\mathbf{E}^0]|\phi^*|$. Let $\phi_{\Re(\nu)}$ be the positive eigenfunction associated to the eigenvalue $r(\mathcal{L}_{\Re(\nu)}[\mathbf{E}^0])$ of the operator $\mathcal{L}_{\Re(\nu)}[\mathbf{E}^0]$. We have $\langle \phi_{\Re(\nu)}, |\phi^*| \rangle \leq \langle \phi_{\Re(\nu)}, \mathcal{L}_\nu[\mathbf{E}^0]|\phi^*| \rangle = r(\mathcal{L}_{\Re(\nu)}[\mathbf{E}^0]) \langle \phi_{\Re(\nu)}, |\phi^*| \rangle$. This implies $r(\mathcal{L}_{\Re(\nu)}[\mathbf{E}^0]) \geq 1$ i.e. $f(\Re(\nu)) \geq f(\nu_0)$ and therefore, $\Re(\nu) \leq \nu_0$. To end the proof of this item, let us show that if $\Re(\nu) = \nu_0$ then $\nu = \nu_0$. We know that $|\phi^*| \leq \mathcal{L}_{\Re(\nu)}[\mathbf{E}^0]|\phi^*| = \mathcal{L}_{\nu_0}[\mathbf{E}^0]|\phi^*|$. If $\mathcal{L}_{\nu_0}[\mathbf{E}^0]|\phi^*| > |\phi^*|$, taking duality pairing with the eigenfunctional G_{ν_0} corresponding to the eigenvalue $r(\mathcal{L}_{\nu_0}[\mathbf{E}^0]) = 1$ on the both sides yields $\langle G_{\nu_0}, \mathcal{L}_{\nu_0}[\mathbf{E}^0]|\phi^*| \rangle = \langle G_{\nu_0}, |\phi^*| \rangle > \langle G_{\nu_0}, |\phi^*| \rangle$ which is a contradiction. Hence, $\mathcal{L}_{\nu_0}[\mathbf{E}^0]|\phi^*| = |\phi^*|$. Then, it follows that there is no element $\nu \in \Sigma$ such that $\Re(\nu) = \nu_0$ and $\nu \neq \nu_0$. ■

We can state the following threshold criterion from the above result.

Lemma 5.3 *The equilibrium $\tilde{\varphi} = (\tilde{\mathbf{S}}, \tilde{\mathbf{I}}(\cdot, \cdot))$ is locally asymptotically stable if $r(\mathcal{L}_0[\tilde{\varphi}]) < 1$ and unstable if $r(\mathcal{L}_0[\tilde{\varphi}]) > 1$.*

Proof. From Lemma 5.2 items (iii) and (iv), we deduce that $\sup \left\{ \Re(\nu) : 1 \in \sigma_p(\mathcal{L}_\nu[\tilde{\varphi}]) \right\} = \nu_0$. Thus $s(A + G[\tilde{\varphi}]) = \sup \left\{ \Re(\nu) : 1 \in \sigma_p(\mathcal{L}_\nu[\tilde{\varphi}]) \right\} < 0$ if $r(\mathcal{L}_0[\tilde{\varphi}]) < 1$ and $s(A + G[\tilde{\varphi}]) = \sup \left\{ \Re(\nu) : 1 \in \sigma_p(\mathcal{L}_\nu[\tilde{\varphi}]) \right\} > 0$ if $r(\mathcal{L}_0[\tilde{\varphi}]) > 1$. ■

5.1 Proof of Theorem 2.7 (i): global stability of the disease-free equilibrium

When the initial condition of System (4.1) satisfies $\varphi_0 \in \partial\mathcal{M}$, i.e., $\sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(b_{i,0}(\tau, x)), \mathbf{I}_{i,0}(\tau, x) \rangle d\tau = 0$, by Claim 5.5, it comes that the semiflow $\Psi(t, \varphi_0)$ generated by system (4.1) is such that $\lim_{t \rightarrow \infty} \Psi(t, \varphi_0) = (\mathbf{S}^0, \mathbf{0}_{L^1(\mathbb{R}, \mathbb{R}^{2n})}, \mathbf{0}_{L^1_+((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})})$.

The local stability of the disease-free equilibrium \mathbf{E}^0 is a direct application of Lemma 5.3. Indeed, at \mathbf{E}^0 , we have $\mathcal{L}_0[\mathbf{E}^0] = \widehat{M}$. It follows that $r(\mathcal{L}_0[\mathbf{E}^0]) = r(\widehat{M})$. From Lemma 5.3, we deduce that if $r(\widehat{M}) = r(\mathcal{L}_0[\mathbf{E}^0]) < 1$ the disease-free equilibrium is locally asymptotically stable and unstable if $r(\widehat{M}) = r(\mathcal{L}_0[\mathbf{E}^0]) > 1$.

It then remain to prove the global stability of the disease-free equilibrium when $r(\widehat{M}) < 1$.

Theorem 5.4 *If $r(\widehat{M}) < 1$ then, the disease-free equilibrium $\mathbf{E}^0 = (\mathbf{S}^0, \mathbf{0}_{L^1((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})})$ of system (4.1) is globally asymptotically stable.*

Proof.

Using the Volterra formulation (4.4) in $\lambda(t, x)$, it comes

$$\begin{aligned} \lambda(t, x) &= \int_{\mathbb{R}} K(x - y) \sum_k \int_0^\infty \langle \beta_k(b_k(\tau, y)), \mathbf{I}_k(t, \tau, y) \rangle d\tau dy \\ &= \int_{\mathbb{R}} K(x - y) \left(\sum_k \int_0^t \langle \beta_k(b_k(\tau, y)), \mathbf{\Pi}_k(\tau, 0, y) \mathbf{p}_k(y) \rangle S_k(t - \tau) \lambda(t - \tau, y) d\tau + f_k(t, y) \right) dy \\ &\leq \int_{\mathbb{R}} K(x - y) \left(S_k^0 \sum_k \int_0^t \langle \beta_k(b_k(\tau, y)), \mathbf{\Pi}_k(\tau, 0, y) \mathbf{p}_k(y) \rangle \lambda(t - \tau, y) d\tau + f_k(t, y) \right) dy, \end{aligned}$$

where

$$f_k(t, x) = \int_t^\infty \langle \beta_k(b_k(\tau, x)), \mathbf{I}_{k0}(\tau - t, x) \rangle d\tau,$$

with $\lim_{t \rightarrow \infty} f_k(t, x) = 0$. It follows that

$$\begin{aligned} \lambda^\infty(x) &\leq \int_{\mathbb{R}} K(x-y) \lambda^\infty(y) \left(\sum_k S_k^0 \int_0^\infty \langle \beta_k(b_k(\tau, y)), \mathbf{\Pi}_k(\tau, 0, y) \mathbf{P}_k(y) \rangle d\tau \right) dy \\ &\leq \int_{\mathbb{R}} K(x-y) \bar{\mathcal{R}}_0(y) \lambda^\infty(y) dy, \end{aligned}$$

where $\lambda^\infty(x) = \limsup_{t \rightarrow \infty} \lambda(t, x)$. We obtain

$$\lambda^\infty(x) \leq \widehat{M}[\lambda^\infty](x). \quad (5.2)$$

Since $r(\widehat{M}) < 1$, then we have $\lambda^\infty(x) = 0$. It follows from (4.4) that $\lim_{t \rightarrow \infty} \mathbf{I}_i(t, \tau, x) = 0$ for all $i \in \mathcal{I}$. This implies that $\lim_{t \rightarrow \infty} \lambda(t, x) = 0$. Then, we are easy to obtain that $\lim_{t \rightarrow \infty} S_i(t) = \frac{\Lambda_i}{\mu_h}$. Hence, we prove the global attractivity of \mathbf{E}^0 . Combining with the above local stability of \mathbf{E}^0 , we obtain that \mathbf{E}^0 is globally asymptotically stable. This completes the proof. \blacksquare

5.2 Proof of Theorem 2.7 (ii): uniform persistence

Our next technical material concerns the uniform persistence of Model (4.1) when $r(\widehat{M}) > 1$ by using the method developed in Theorem 5.2 in [41]. For the invariant sets of uniform persistence, we introduce

$$\mathcal{M} = \mathbb{R}^n \times \{\mathbf{0}_{L^1(\mathbb{R}, \mathbb{R}^{2n})}\} \times \mathcal{M}_I, \quad \text{and} \quad \partial\mathcal{M} = \mathcal{X}_{0+} \setminus \mathcal{M},$$

where

$$\mathcal{M}_I = \left\{ \mathbf{I} \in L^1_+((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n}) : \int_{\mathbb{R}} \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(b_i(\tau, x)), \mathbf{I}_i(\tau, x) \rangle d\tau dx > 0 \right\}.$$

For the unique solution $\varphi = (\mathbf{S}, \mathbf{0}_{L^1}, \mathbf{I})$ of system (4.1) associated to the initial condition $\varphi_0 = (\mathbf{S}_0, \mathbf{0}_{L^1}, \mathbf{I}_0(\cdot, \cdot)) \in \mathcal{M}$, we define $\Psi(t, \varphi_0) = (\mathbf{S}(t), \mathbf{0}_{L^1}, \mathbf{I}(t, \cdot, \cdot))$ the semiflow of Model (4.1) passing through φ_0 . Next, we first claim that

Claim 5.5 *The subsets \mathcal{M} and $\partial\mathcal{M}$ are positively invariant with respect to the semiflow $\Psi(t, \cdot)$ generated by system (4.1). Furthermore, $\lim_{t \rightarrow \infty} \Psi(t, \varphi_0) = (\mathbf{S}^0, \mathbf{0}_{L^1(\mathbb{R}, \mathbb{R}^{2n}), \mathbf{0}_{L^1_+((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n}))})^T$ for each $\varphi_0 \in \partial\mathcal{M}$.*

Proof of Claim 5.5. Let $\varphi_0 = (\mathbf{S}_0, \mathbf{0}_{L^1}, \mathbf{I}_0(\cdot, \cdot))^T \in \mathcal{M}$ be given and $\Psi(t, \varphi_0) = (\mathbf{S}, \mathbf{0}_{L^1}, \mathbf{I}(t, \cdot, \cdot))^T$, the orbit passing through φ_0 . Since $\varphi_0 \in \mathcal{M}$, then $\int_{\mathbb{R}} \bar{\lambda}(0, x) dx > 0$. Through a direct calculation, we have

$$\begin{aligned} \partial_t \lambda(t, x) &= \int_{\mathbb{R}} K(x-y) \sum_{i \in \mathcal{I}} \int_0^\infty \langle \beta_i(b_i(\tau, y)), \partial_t \mathbf{I}_i(\tau, y) \rangle d\tau dy, \\ &\geq -(\bar{\alpha}_0 + \omega_0 + \mu_h) \lambda(t, x), \end{aligned}$$

where $\bar{\alpha}_0 = \max\{\alpha_i^T, \alpha_i^U\}$ and $\omega_0 = \max\{\bar{\omega}_T^U, \bar{\omega}_U^T\}$. Thus, one obtain that

$$\lambda(t, x) \geq e^{-(\bar{\alpha}_0 + \omega_0 + \mu_h)t} \lambda(0, x) > 0,$$

for $t \geq 0$. This complete the fact that \mathcal{M} is positively invariant.

Now, let $\varphi_0 \in \partial\mathcal{M}$. Since for all $i \in \mathcal{I}$, $S_i(t) \leq S_i^0$ as t is large enough, the comparison principle implies that

$$\mathbf{I}_i(t, \tau, x) \leq \tilde{\mathbf{I}}_i(t, \tau, x), \quad \forall i \in \mathcal{I}, \quad (5.3)$$

where $\tilde{\mathbf{I}}_i(t, \tau, x)$ is the solution of the following system

$$\begin{cases} \tilde{\mathbf{I}}_i(t, \tau = 0, x) = \mathbf{p}_i(x) \tilde{\lambda}(t, x) S_i^0, \\ \tilde{\mathbf{I}}_i(0, \tau, x) = \mathbf{I}_{i0}(\tau, x), \\ (\partial_t + \partial_\tau) \tilde{\mathbf{I}}_i(t, \tau, x) = (\boldsymbol{\omega}(\tau, x) - \boldsymbol{\alpha}_i(b_i(\tau, x)) - \mu_h) \tilde{\mathbf{I}}_i(t, \tau, x). \end{cases} \quad (5.4)$$

By the Volterra formulation, we have from (5.4) that

$$\tilde{\mathbf{I}}_i(t, \tau, x) = \begin{cases} \mathbf{\Pi}_i(\tau, \tau - t, x) \mathbf{I}_{i0}(\tau - t, x), & \text{if } t \leq \tau, \\ \mathbf{\Pi}_i(\tau, 0, x) \mathbf{p}_i(x) S_i^0 \tilde{\lambda}(t - \tau, x), & \text{if } t > \tau, \end{cases}$$

where $\tilde{\lambda}(t, x)$ satisfies

$$\begin{aligned} \tilde{\lambda}(t, x) &= \int_{\mathbb{R}} K(x - y) \sum_{k \in \mathcal{I}} S_k^0 \int_0^t \langle \boldsymbol{\beta}_k(b_k(\tau, y)), \mathbf{\Pi}_k(\tau, 0, y) \mathbf{p}_k(y) \rangle \tilde{\lambda}(t - \tau, y) d\tau dy \\ &\quad + \int_{\mathbb{R}} K(x - y) \sum_{k \in \mathcal{I}} \int_t^\infty \langle \boldsymbol{\beta}_k(b_k(\tau, y)), \mathbf{\Pi}_k(\tau, \tau - t, y) \mathbf{I}_{k0}(\tau - t, y) \rangle d\tau dy. \end{aligned}$$

The initial condition with $\sum_{k \in \mathcal{I}} \int_0^\infty \langle \boldsymbol{\beta}_k(b_k(\tau, x)), \mathbf{I}_{k0}(\tau, x) \rangle d\tau = 0$, leads to

$$\tilde{\lambda}(t, x) = \int_{\mathbb{R}} K(x - y) \sum_{k \in \mathcal{I}} S_k^0 \int_0^t \langle \boldsymbol{\beta}_k(b_k(\tau, y)), \mathbf{\Pi}_k(\tau, 0, y) \mathbf{p}_k(y) \rangle \tilde{\lambda}(t - \tau, y) d\tau dy.$$

Since $\tilde{\lambda}(0, \cdot) = 0$, we have $\tilde{\lambda}(t, \cdot) = 0$ for all $t \geq 0$, and then $\tilde{\mathbf{I}}_i(t, \cdot, \cdot) = 0$ for all $i \in \mathcal{I}$ and $t \geq 0$. The comparison in (5.3) implies that $\mathbf{I}_i(t, \cdot, \cdot) = 0$ for all $i \in \mathcal{I}$ and $t \geq 0$ and then $\partial\mathcal{M}$ is positively invariant under the semiflow $\Psi(t, \cdot)$. In addition, it is clear for the solution remaining in $\partial\mathcal{M}$, we have for all $i \in \mathcal{I}$, $S_i \rightarrow S_i^0$. Hence, $\lim_{t \rightarrow \infty} \Psi(t, \varphi_0) = (\mathbf{S}^0, \mathbf{0}_{L^1(\mathbb{R}, \mathbb{R}^{2n})}, \mathbf{0}_{L^1_+((0, \infty) \times \mathbb{R}, \mathbb{R}^{2n})})^T$ for each $\varphi_0 \in \partial\mathcal{M}$. This ends the proof of Claim 5.5. \blacksquare

Finally, we end this technical material section by establishing the uniform persistence of system (4.1).

Theorem 5.6 *The semiflow $\{\Psi(t, \cdot)\}_{t \geq 0}$ generated by system (4.1) is uniformly persistent in \mathcal{M} with respect to $(\mathcal{M}, \partial\mathcal{M})$, that is, there exists a constant $\eta > 0$ such that for each $\varphi_0 \in \mathcal{M}$,*

$$\liminf_{t \rightarrow \infty} \mathbf{S}(t) \geq \eta,$$

and

$$\liminf_{t \rightarrow \infty} \|\mathbf{I}(t, \cdot, \cdot)\|_{L^1_+} \geq \eta \quad \text{whenever } r(\widehat{M}) > 1.$$

Furthermore, there exists compact global attractor \mathcal{A}_1 in \mathcal{M} for the semiflow $\{\Psi(t, \cdot)\}_{t \geq 0}$.

Proof. In the following, we will prove that $W^S(\{\mathbf{E}^0\}) \cap \mathcal{M} = \emptyset$, where

$$W^S(\{\mathbf{E}^0\}) = \{\varphi_0 \in \mathcal{X}_{0+} : \lim_{t \rightarrow +\infty} \Psi(t, \varphi_0) = \mathbf{E}^0\}.$$

Since from Claim 5.5 the disease-free equilibrium \mathbf{E}^0 is globally asymptotically stable in $\partial\mathcal{M}$, we need only to study the behavior of the solution starting in \mathcal{M} in some neighborhood of \mathbf{E}^0 . To this end, it is

sufficient to show that there exists $\sigma > 0$ satisfying for each $\varphi \in \{\mathbf{v} \in \mathcal{M} : \|\mathbf{E}^0 - \mathbf{v}\| \leq \sigma\}$ there exists $t_0 \geq 0$ such that $\|\Psi(t, \varphi_0) - \mathbf{E}^0\| > \sigma$.

By the way of contradiction, suppose that for each integer $n \geq 0$ there exists a $\varphi_0^n = (\mathbf{S}_0^n, \mathbf{0}_{L^1}, \mathbf{I}_0^n) \in \{\mathbf{v} \in \mathcal{M} : \|\mathbf{E}^0 - \mathbf{v}\| \leq \sigma\}$ such that

$$\|\mathbf{E}^0 - \Psi(t, \varphi_0^n)\| \leq \frac{1}{n+1}, \quad \forall t \geq 0.$$

Denote $\Psi(t, \varphi_0^n) = (\mathbf{S}^n(t), \mathbf{0}_{L^1}, \mathbf{I}^n(t, \cdot, \cdot))$, then for all $t \geq 0$ we have

$$|\mathbf{S}^n(t) - \mathbf{S}^0| \leq \frac{1}{n+1}, \quad \forall t \geq 0. \quad (5.5)$$

It follows that for all i , we have $S_i^n(t) \geq S_i^0 - \frac{1}{n+1}$ for all $t \geq 0$. Consider the following system

$$\begin{cases} (\partial_t + \partial_\tau) \mathbf{I}^n(t, \tau, x) = \text{diag}(\Phi(\tau, x)) \mathbf{I}^n(t, \tau, x), \\ \mathbf{I}^n(t, 0, x) = \lambda^n(t, x) \text{diag}(\mathbf{S}^n(t)) \mathbf{p}(x), \\ \mathbf{S}^n(0) = \mathbf{S}_0^n, \quad \mathbf{I}^n(0, \cdot, \cdot) = \mathbf{I}_0^n(\cdot, \cdot), \quad (\mathbf{S}_0^n, \mathbf{I}_0^n) \in \mathcal{M}, \end{cases}$$

where $\Phi(\tau, x) = (\Phi_i(\tau, x))_i$ with $\Phi_i(\tau, x) = \omega(\tau, x) - \alpha_i(b_i(\tau, x)) - \mu_h$, $\mathbf{p}(x) = (\mathbf{p}_i(x))_i$, $\lambda^n(t, x) = \sum_i \int_0^t \langle \beta_i(b_i(\tau, x)), \mathbf{I}_i^n(t, \tau, x) \rangle d\tau$, $\mathbf{S}_0^n = (\mathbf{S}_{i0}^n)_i$ and $\mathbf{I}_0^n(\cdot, \cdot) = (\mathbf{I}_{i0}^n(\cdot, \cdot))_i$. By the comparison principle, we have

$$\mathbf{I}^n(t, \cdot, \cdot) \geq \tilde{\mathbf{I}}^n(t, \cdot, \cdot), \quad (5.6)$$

where $\tilde{\mathbf{I}}^n(t, \cdot, \cdot)$ is the solution of the following auxiliary system

$$\begin{cases} (\partial_t + \partial_\tau) \tilde{\mathbf{I}}^n(t, \tau, x) = \text{diag}(\Phi(\tau, x)) \tilde{\mathbf{I}}^n(t, \tau, x), \\ \tilde{\mathbf{I}}^n(t, 0, x) = \tilde{\lambda}^n(t, x) \text{diag} \left(\mathbf{S}^0 - \frac{1}{n+1} I \right) \mathbf{p}(x), \\ \tilde{\mathbf{I}}^n(0, \cdot, \cdot) = \mathbf{I}_0^n(\cdot, \cdot), \end{cases}$$

which gives for all i ,

$$\begin{cases} (\partial_t + \partial_\tau) \tilde{\mathbf{I}}_i^n(t, \tau, x) = \Phi_i(\tau, x) \tilde{\mathbf{I}}_i^n(t, \tau, x), \\ \tilde{\mathbf{I}}_i^n(t, 0, x) = \tilde{\lambda}^n(t, x) \left(\mathbf{S}_i^0 - \frac{1}{n+1} \right) \mathbf{p}_i(x), \\ \tilde{\mathbf{I}}_i^n(0, \cdot, \cdot) = \mathbf{I}_{i0}^n(\cdot, \cdot). \end{cases} \quad (5.7)$$

For ease of notation, let us rewrite the system (5.7) as the following form :

$$\frac{d\tilde{\mathbf{v}}_i^n(t)}{dt} = \left(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n \right) \tilde{\mathbf{v}}_i^n(t), \quad \forall t \geq 0, \quad (5.8)$$

$\tilde{\mathbf{v}}_i^n(0) \in \overline{D(\tilde{A}_i^n)}$, the closure of $D(\tilde{A}_i^n) = \{\mathbf{0}_{L^1(\mathbb{R}, \mathbb{R}^2)}\} \times W^{1,1}((0, \infty) \times \mathbb{R}, \mathbb{R}^2)$, where $\tilde{\mathbf{v}}_i^n(t) = (\mathbf{0}_{L^1}, \tilde{\mathbf{I}}_i^n(t, \cdot, \cdot))^t$ and the operators \tilde{A}_i^n and $\tilde{\mathcal{L}}_i^n$ are defined as

$$\tilde{A}_i^n(\mathbf{0}_{L^1}, \tilde{\mathbf{I}}_i^n) = \left(-\tilde{\mathbf{I}}_i^n(0, x), -\partial_\tau \tilde{\mathbf{I}}_i^n + \Phi_i(\tau, x) \tilde{\mathbf{I}}_i^n \right)$$

and

$$\tilde{\mathcal{L}}_i^n(\mathbf{0}_{L^1}, \tilde{\mathbf{I}}_i^n) = \left(\tilde{\lambda}^n(t, x) \left(\mathbf{S}_i^0 - \frac{1}{n+1} \right) \mathbf{p}_i(x), \mathbf{0}_{L^1((0, \infty) \times \mathbb{R}, \mathbb{R}^2)} \right).$$

Note that the semigroup $\left\{T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)}(t)\right\}_{t \geq 0}$ generated by (5.8) is irreducible. Similarly to the proof of Lemma 4.6, we can derive the set of characteristic values for system (5.7) as

$$\Sigma_n := \left\{ \nu \in \mathbb{C} : 1 \in \sigma_p \left(\mathcal{L}_\nu \left[\mathbf{E}^0 - \frac{1}{n+1} I \right] \right) \right\}. \quad (5.9)$$

Since $r(\widehat{M}) = r(\mathcal{L}_0[\mathbf{E}^0]) > 1$, there exists a $n > 0$ large enough such that

$$r(\widehat{M}_n) = r \left(\mathcal{L}_0 \left[\mathbf{E}^0 - \frac{1}{n+1} I \right] \right) > 1.$$

Therefore, from Lemma 5.2, there exists a dominant eigenvalue ν_n^* of Σ_n such that $r \left(\mathcal{L}_{\nu_n^*} \left[\mathbf{E}^0 - \frac{1}{n+1} I \right] \right) = 1$ with $\nu_n^* > 0$. $\nu_n^* > 0$ is a simple dominant eigenvalue of $(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)$. From Lemma (4.6), we have shown that $\omega_{0,ess}(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n) \leq -\mu_h$. Moreover, the semigroup $\left\{T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)}(t)\right\}_{t \geq 0}$ is irreducible. It follows from Corollary 4.6.8 in [35] that $\left\{T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)}(t)\right\}_{t \geq 0}$ has asynchronous exponential growth with intrinsic growth constant $\nu_n^* \in \mathbb{R}$. Therefore, using Theorem 3.9 in [33], we have

$$T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)_0}(t) \tilde{\Pi}_{\nu_n^*} = \tilde{\Pi}_{\nu_n^*} T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)_0}(t) = e^{\nu_n^* t} \tilde{\Pi}_{\nu_n^*}, \quad \forall t \geq 0,$$

and there exist constants $\epsilon_0 > 0$ and $\eta_0 > 0$ such that

$$\|T_{(\tilde{A}_i^n + \tilde{\mathcal{L}}_i^n)_0}(t) (I - \tilde{\Pi}_{\nu_n^*})\| \leq \eta_0 e^{(\nu_n^* - \epsilon_0)t} \|(I - \tilde{\Pi}_{\nu_n^*})\|, \quad \forall t \geq 0,$$

where $\tilde{\Pi}_{\nu_n^*}$ is the projector on the generalized eigenspace associated with the largest eigenvalue $\nu_n^* > 0$. We deduce that

$$\tilde{\Pi}_{\nu_n^*} \tilde{v}_i^n(t) = e^{\nu_n^* t} \tilde{\Pi}_{\nu_n^*} \tilde{v}_{i0}^n.$$

Since $\nu_n^* > 0$, it follows that $\lim_{t \rightarrow \infty} \|\tilde{\Pi}_{\nu_n^*} \tilde{v}_i^n(t)\|_{L^1} = +\infty$. Therefore, $\lim_{t \rightarrow \infty} \|\tilde{\mathbf{I}}_i^n(t, \cdot, \cdot)\|_{L^1} = +\infty$ and from (5.6), we have $\lim_{t \rightarrow \infty} \|\mathbf{I}_i^n(t, \cdot, \cdot)\|_{L^1} = +\infty$, which is a contradiction to the boundedness of the solution. Thus, $W^S(\{\mathbf{E}^0\}) \cap \mathcal{M} = \emptyset$ and we derive from Theorem 4.2 in [25] that the semiflow $\{\Psi(t, \cdot)\}_{t \geq 0}$ is uniform persistent with respect to the pair $(\mathcal{M}, \partial\mathcal{M})$. Moreover, by Theorem 3.7 in [36], there exists a compact global attractor $\mathcal{A}_1 \subset \mathcal{M}$ for the semiflow $\{\Psi(t, \cdot)\}_{t \geq 0}$. ■

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Conflict of interest disclosure

The authors of this article declare that they have no financial conflict of interest with the content of this article.

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